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MAY 1992

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Volume 49, Number 5

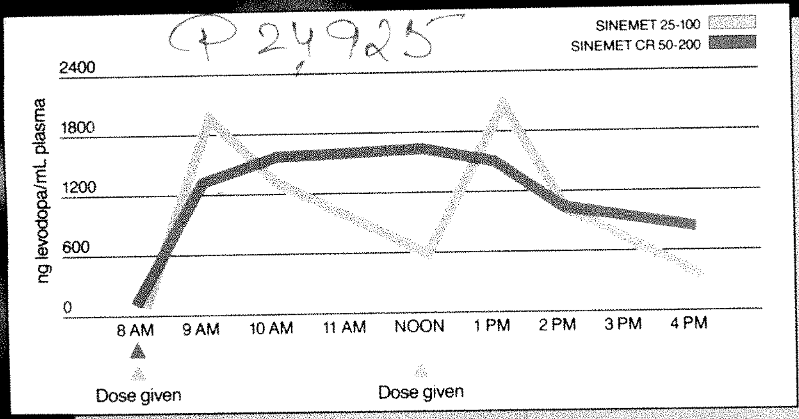
American Medical Association
Physicians dedicated to the health of America

For many patients with
Parkinson's disease

More Quality Time*

The causes of motor fluctuations are not completely understood; *in some patients* they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.

P 24925



Smoother plasma levodopa levels[†][1]

Less fluctuation of plasma levodopa levels with SINEMET CR vs SINEMET® (Carbidopa-Levodopa)

In a clinical trial, 14 patients with mild to moderate Parkinson's disease had plasma levodopa levels measured over 8 hours after one dose of SINEMET CR, and were compared with levels over the same period after two doses of SINEMET 25-100.

SINEMET® CR
(CARBIDOPA-LEVODOPA)
SUSTAINED-RELEASE

Before prescribing SINEMET CR, please see a Brief Summary of Full Prescribing Information on the third page of this advertisement.

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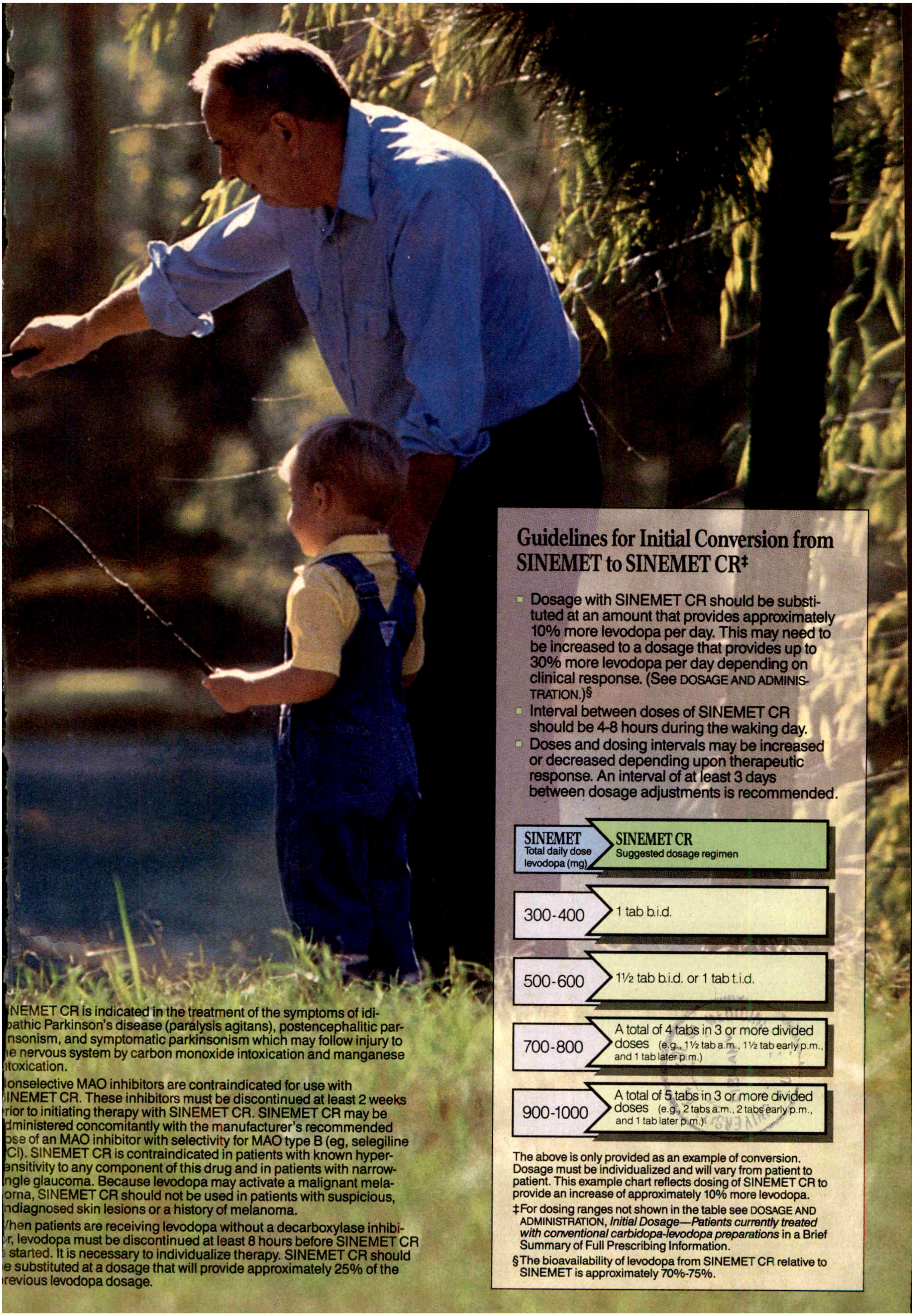
[*] Although in clinical trials, patients with moderate to severe motor fluctuations who received SINEMET® CR (Carbidopa-Levodopa) Sustained-Release *did not experience quantitatively significant reductions* in "off" time when compared to SINEMET, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET.

[†] Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET. The physician should be notified if such delayed responses pose a problem in treatment.

1. Goetz CG, Tanner CM, Shannon KM, et al. Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuations. *Neurology.* 1988;38:1143-1146.



Guidelines for Initial Conversion from SINEMET to SINEMET CR‡

- Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day. This may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response. (See DOSAGE AND ADMINISTRATION.)§
- Interval between doses of SINEMET CR should be 4-8 hours during the waking day.
- Doses and dosing intervals may be increased or decreased depending upon therapeutic response. An interval of at least 3 days between dosage adjustments is recommended.

SINEMET Total daily dose levodopa (mg)	**SINEMET CR** Suggested dosage regimen
300-400	1 tab b.i.d.
500-600	1½ tab b.i.d. or 1 tab t.i.d.
700-800	A total of 4 tabs in 3 or more divided doses (e.g., 1½ tab a.m., 1½ tab early p.m., and 1 tab later p.m.)
900-1000	A total of 5 tabs in 3 or more divided doses (e.g., 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

The above is only provided as an example of conversion. Dosage must be individualized and will vary from patient to patient. This example chart reflects dosing of SINEMET CR to provide an increase of approximately 10% more levodopa.

‡For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage—Patients currently treated with conventional carbidopa-levodopa preparations* in a Brief Summary of Full Prescribing Information.

§The bioavailability of levodopa from SINEMET CR relative to SINEMET is approximately 70%-75%.

NEMET CR is indicated in the treatment of the symptoms of idi-
pathic Parkinson's disease (paralysis agitans), postencephalitic par-
nsonism, and symptomatic parkinsonism which may follow injury to
e nervous system by carbon monoxide intoxication and manganese
toxication.

onselective MAO inhibitors are contraindicated for use with
INEMET CR. These inhibitors must be discontinued at least 2 weeks
rior to initiating therapy with SINEMET CR. SINEMET CR may be
dministered concomitantly with the manufacturer's recommended
ose of an MAO inhibitor with selectivity for MAO type B (eg, selegiline
Cl). SINEMET CR is contraindicated in patients with known hyper-
ensitivity to any component of this drug and in patients with narrow-
ngle glaucoma. Because levodopa may activate a malignant mela-
oma, SINEMET CR should not be used in patients with suspicious,
ndiagnosed skin lesions or a history of melanoma.

hen patients are receiving levodopa without a decarboxylase inhibi-
r, levodopa must be discontinued at least 8 hours before SINEMET CR
started. It is necessary to individualize therapy. SINEMET CR should
e substituted at a dosage that will provide approximately 25% of the
revious levodopa dosage.

SINEMET® CR (CARBIDOPA-LEVODOPA)

SUSTAINED-RELEASE TABLETS

CONTRAINDICATIONS Nonselective MAO inhibitors are contraindicated for use with SINEMET* CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl).

SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least eight hours before SINEMET CR is started. In order to reduce adverse reactions, it is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION).

Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, will occur at lower dosages and sooner during therapy with SINEMET CR (Carbidopa-Levodopa, Sustained-Release) than with levodopa alone.

As with levodopa, SINEMET CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution. The occurrence of dyskinesias may require dosage reduction.

Patients receiving SINEMET CR may develop increased dyskinesia compared to SINEMET (Carbidopa-Levodopa).

SINEMET CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET CR to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET CR may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

PRECAUTIONS General As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET CR provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Information for Patients The patient should be informed that SINEMET CR is a sustained-release formulation of carbidopa-levodopa which releases these ingredients over a 4 to 6 hour period. It is important that SINEMET CR be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

If abnormal involuntary movements appear or get worse during treatment with SINEMET CR, the physician should be notified, as dosage adjustment may be necessary.

Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET (Carbidopa-Levodopa). The physician should be notified if such delayed responses pose a problem in treatment.

Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.

NOTE: The suggested advice to patients being treated with SINEMET CR is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Laboratory Tests Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa-levodopa preparations than with levodopa.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions *Caution should be exercised when the following drugs are administered concomitantly with SINEMET CR (Carbidopa-Levodopa, Sustained-Release).*

Symptomatic postural hypotension has occurred when carbidopa-levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with SINEMET CR is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET CR should be carefully observed for loss of therapeutic response.

Carcinogenesis, Mutagenesis, Impairment of Fertility In a two-year bioassay of SINEMET (Carbidopa-Levodopa), no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

In reproduction studies with SINEMET (Carbidopa-Levodopa), no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

Pregnancy Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET (Carbidopa-Levodopa). There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. SINEMET (Carbidopa-Levodopa) caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. Use of SINEMET CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINEMET CR is administered to a nursing mother.

Pediatric Use Safety and effectiveness in infants and children have not been established, and use of the drug in patients below the age of 18 is not recommended.

ADVERSE REACTIONS In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations while on SINEMET (Carbidopa-Levodopa) were randomized to therapy with either SINEMET (Carbidopa-Levodopa) or SINEMET CR. The adverse experience frequency profile of SINEMET CR did not differ substantially from that of SINEMET (Carbidopa-Levodopa), as shown in Table 1.

Table 1 Clinical Adverse Experiences Occurring in 1% or Greater of Patients

Adverse Experience	**SINEMET CR** n=491 %	**SINEMET** (Carbidopa-Levodopa) n=524 %
Dyskinesia	16.5	12.2
Nausea	5.5	5.7
Hallucinations	3.9	3.2
Confusion	3.7	2.3
Dizziness	2.9	2.3
Depression	2.2	1.3
Urinary Tract Infection	2.2	2.3
Headache	2.0	1.9
Dream Abnormalities	1.8	0.8
Dystonia	1.8	0.8
Vomiting	1.8	1.9
Upper Respiratory Infection	1.8	1.0
Dyspnea	1.6	0.4
'On-Off' Phenomena	1.6	1.1
Back Pain	1.6	0.6
Dry Mouth	1.4	1.1
Anorexia	1.2	1.1
Diarrhea	1.2	0.6
Insomnia	1.2	1.0
Orthostatic Hypotension	1.0	1.1
Shoulder Pain	1.0	0.6
Chest Pain	1.0	0.8
Muscle Cramps	0.8	1.0
Paresthesia	0.8	1.1
Urinary Frequency	0.8	1.1
Dyspepsia	0.6	1.1
Constipation	0.2	1.5

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received SINEMET CR and 475 who received SINEMET (Carbidopa-Levodopa) during controlled clinical trials included: decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.

The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with SINEMET CR, listed by body system in order of decreasing frequency, include:

Nervous System/Psychiatric: Chorea, somnolence, falling, anxiety disorder, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.

Body as a Whole: Asthenia, fatigue, abdominal pain, orthostatic effects.

Digestive: Gastrointestinal pain, dysphagia, heartburn.

Cardiovascular: Palpitation, essential hypertension, hypotension, myocardial infarction.

Special Senses: Blurred vision.

Metabolic: Weight loss.

Skin: Rash.

Respiratory: Cough, pharyngeal pain, common cold.

Urogenital: Urinary incontinence.

Musculoskeletal: Leg pain.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

Other adverse experiences have been reported with various carbidopa-levodopa formulations and may occur with SINEMET CR:

Nervous System/Psychiatric: Mental changes including paranoid ideation, psychotic episodes, depression with suicidal tendencies and dementia; convulsions (however, a causal relationship has not been established); bradykinetic episodes.

Gastrointestinal: Gastrointestinal bleeding, development of duodenal ulcer.

Cardiovascular: Cardiac irregularities, phlebitis.

Hematologic: Hemolytic and nonhemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.

Laboratory Tests: Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, protein-bound iodine, Coombs test.

Other adverse reactions that have been reported with levodopa are:

Nervous System: Numbness, increased hand tremor, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome.

Psychiatric: Delusions, euphoria.

Gastrointestinal: Bitter taste, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.

Metabolic: Weight gain, edema.

Integumentary: Malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, loss of hair.

Genitourinary: Urinary retention, urinary incontinence, dark urine, priapism.

Miscellaneous: Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE Management of acute overdosage with SINEMET CR is the same as with levodopa. Pyridoxine is not effective in reversing the actions of SINEMET CR.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET CR should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION SINEMET CR tablets contain carbidopa (50 mg) and levodopa (200 mg) in a 1:4 ratio. The daily dosage of SINEMET C must be determined by careful titration. Patients should be monitored clos ing the dose adjustment period, particularly with regard to appearance or wo ing of involuntary movements, dyskinesias or nausea. SINEMET CR may administered as whole or as half-tablets which should not be chewed or crushe

Standard drugs for Parkinson's disease, other than levodopa without a decarbo ylase inhibitor, may be used concomitantly while SINEMET CR is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Initial Dosage *Patients currently treated with conventional carbidopa-levodopa preparations:* Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see DOSAGE AND ADMINISTRATION, TITRATION). The interval between doses of SINEMET CR should be 4-8 hours during the waking day. *Patients currently treated with levodopa without a decarboxylase inhibitor:* Levodopa must be discontinued at least eight hours before therapy with SINEMET CR is started. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET CR b.i.d. *Patients not receiving levodopa:* In patients with mild to moderate disease, the initial recommended dose is 1 tablet of SINEMET CR b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with 2 to 8 tablets per day, administered as divided doses at intervals ranging from 4 to 8 hours during the waking day. Higher doses (12 or more tablets per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day.

An interval of at least 3 days between dosage adjustments is recommended.

Maintenance Because Parkinson's disease is progressive, periodic clinical evaluations are recommended; adjustment of the dosage regimen of SINEMET CR may be required.

Addition of Other Antiparkinson Medications Anticholinergic agents, dopamine agonists, and amantadine can be given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added.

A dose of SINEMET (Carbidopa-Levodopa) 25-100 or 10-100 (one half or a whole tablet) can be added to the dosage regimen of SINEMET CR in selected patients with advanced disease who need additional levodopa for a brief time during daytime hours.

Interruption of Therapy Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET CR is required, especially if the patient is receiving neuroleptics. (See WARNINGS).

If general anesthesia is required, SINEMET CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED SINEMET CR 50-200 (Carbidopa-Levodopa) SUSTAINED-RELEASE TABLETS containing 50 mg of carbidopa and 200 mg of levodopa, are peach-colored, oval, scored, biconvex, compressed tablets, coded 521. They are supplied as follows:

NDC 0056-0521-68 bottles of 100

NDC 0056-0521-28 unit dose packages of 100.

Storage Avoid temperatures above 30°C (86°F). Store in a tightly closed container.

A.H.F.S. Category: 92:00 Issued June 1991 Printed in U.S.A.

Manufactured by:

MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA
FOR:

DU PONT
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Du Pont Pharmaceuticals
Wilmington, DE 19880-0026

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Brief Summary of 6251-3/7619403 CR-3123

TABLETS

SINEMET® (CARBIDOPA-LEVODOPA)

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS (below) and DOSAGE AND ADMINISTRATION sections in the Prescribing Information before initiating therapy.

INDICATIONS: SINEMET is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication. SINEMET is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B_6).

The incidence of levodopa-induced nausea and vomiting is less with SINEMET than with levodopa. In many patients this reduction in nausea and vomiting will permit more rapid dosage titration.

In some patients a somewhat smoother antiparkinsonian effect results from therapy with SINEMET than with levodopa. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from SINEMET.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Although the administration of carbidopa permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa. *Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, may occur at low dosages and sooner during therapy with SINEMET than with levodopa.*

Certain patients who responded poorly to levodopa have improved when SINEMET was substituted. This is most likely due to decreased peripheral decarboxylation of levodopa which results from administration of carbidopa rather than to a primary effect of carbidopa on the nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa in parkinsonian syndromes.

In considering whether to give SINEMET to patients already on levodopa who have nausea and/or vomiting, the practitioner should be aware that, while many patients may be expected to improve, some do not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing SINEMET with levodopa, about half of the patients with nausea and/or vomiting on levodopa improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

CONTRAINDICATIONS: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See DOSAGE AND ADMINISTRATION section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

PRECAUTIONS: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS (above).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

ADVERSE REACTIONS: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitation, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic an non-hemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred

Laboratory tests which have been reported to be abnormal are alkaline phosphatas SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, protei bound iodine, and Coombs test.

Other adverse reactions that have been reported with levodopa are: *Nervous System* ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps blepharospasm (which may be taken as an early sign of excess dosage, conside ation of dosage reduction may be made at this time), trismus, activation of later Horner's syndrome. *Psychiatric:* confusion, sleepiness, insomnia, nightmares, ha lucinations, delusions, agitation, anxiety, euphoria. *Gastrointestinal:* dry mouth, bitte taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, con stipation, diarrhea, flatulence, burning sensation of tongue. *Metabolic:* weight gai or loss, edema. *Integumentary:* malignant melanoma (see also CONTRA INDICATIONS), flushing, increased sweating, dark sweat, skin rash, loss of ha *Genitourinary:* urinary retention, urinary incontinence, dark urine, priapism. *Spe cial Senses:* diplopia, blurred vision, dilated pupils, oculogyric crises. *Miscella ous:* weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sens of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

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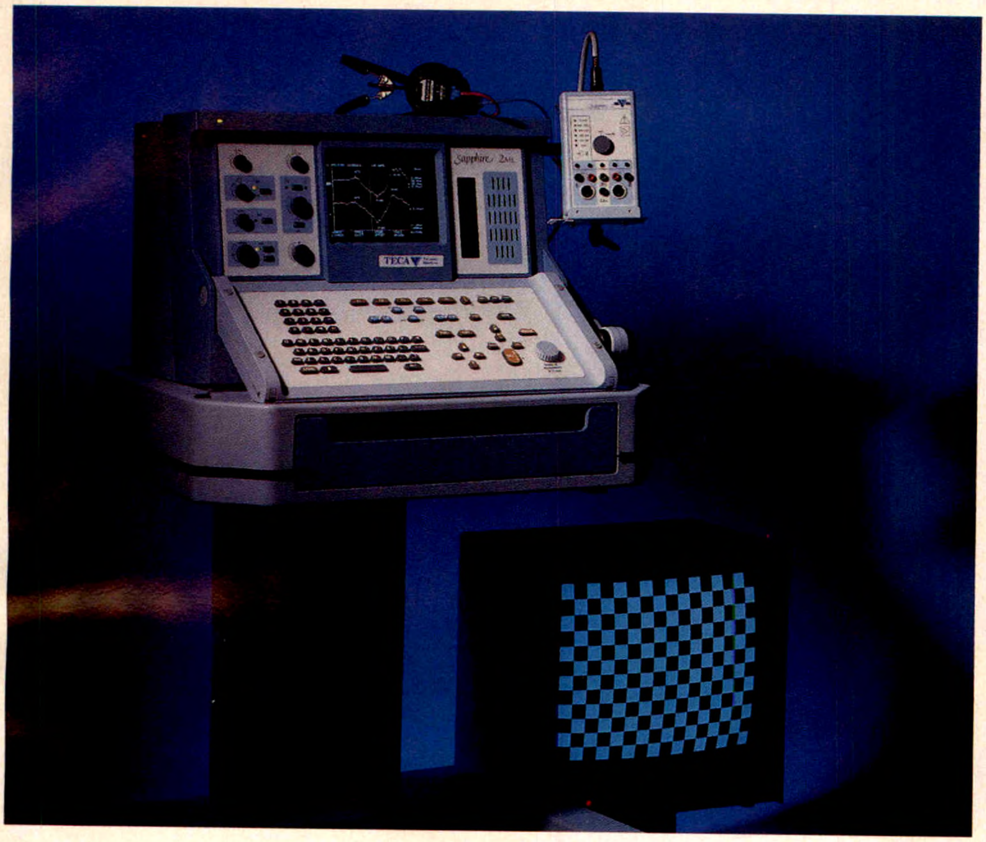

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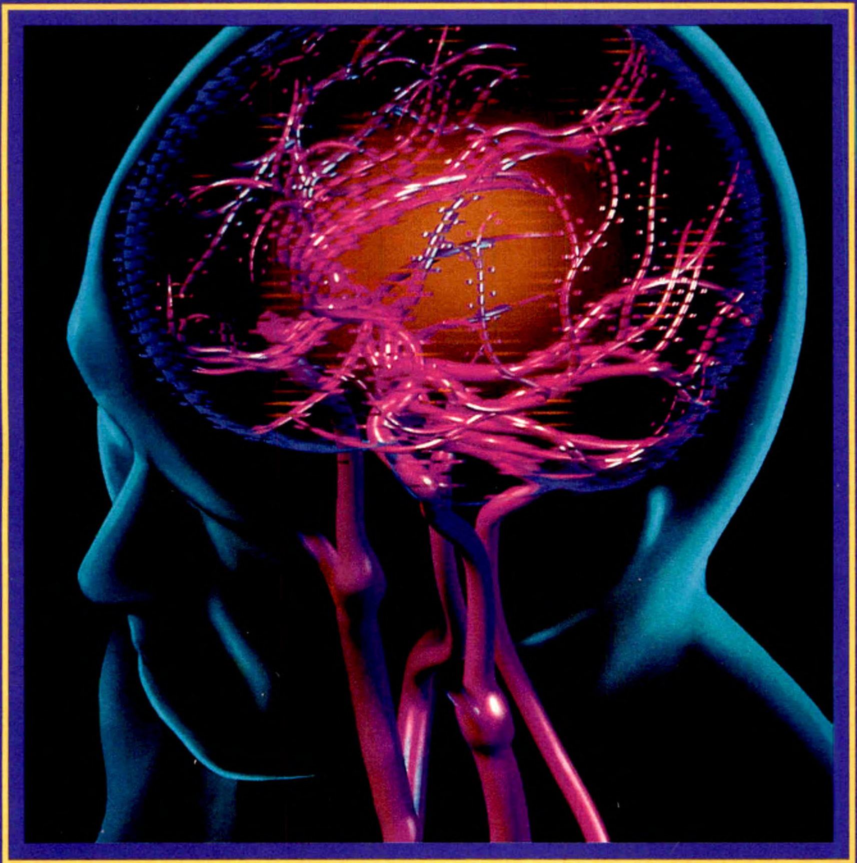

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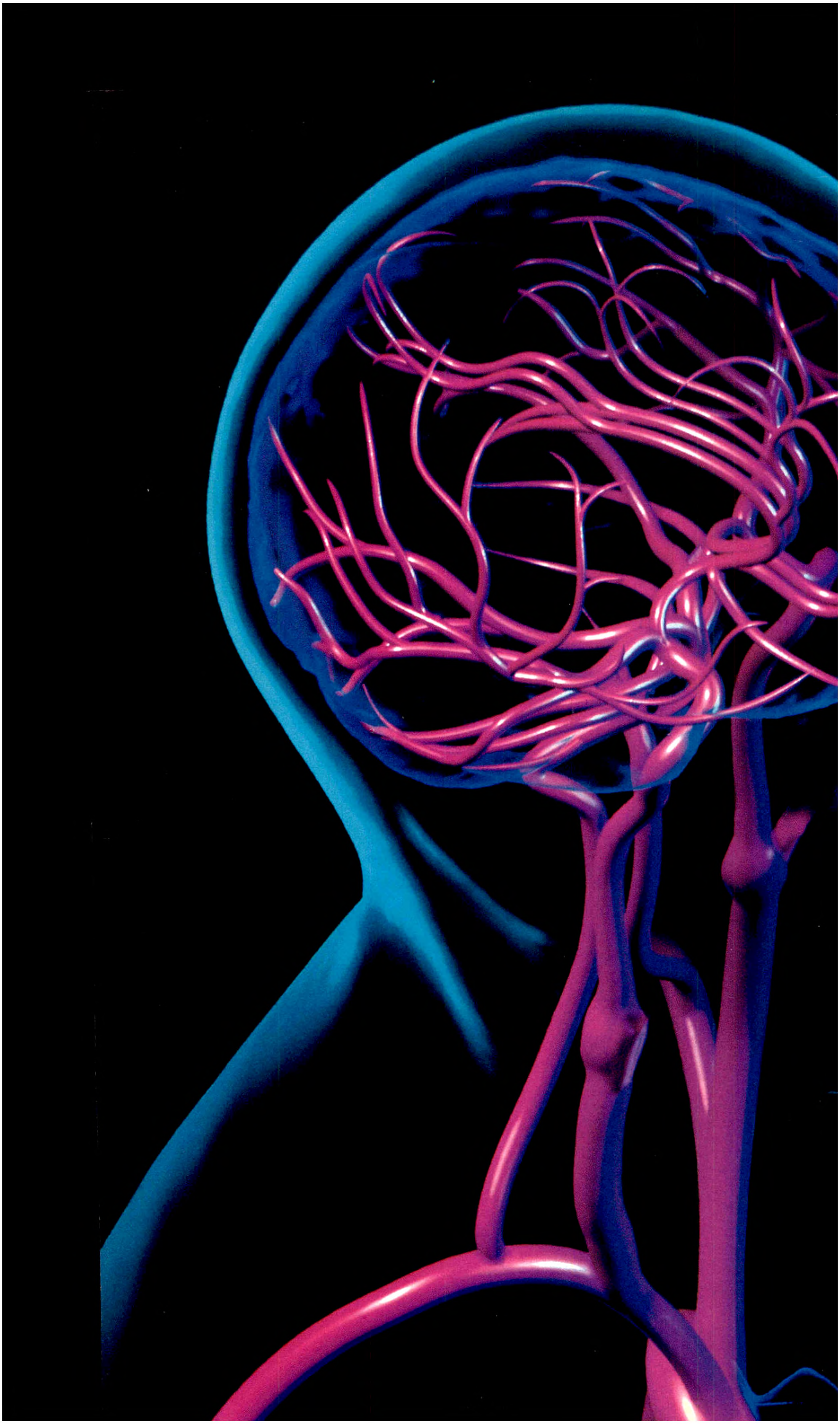

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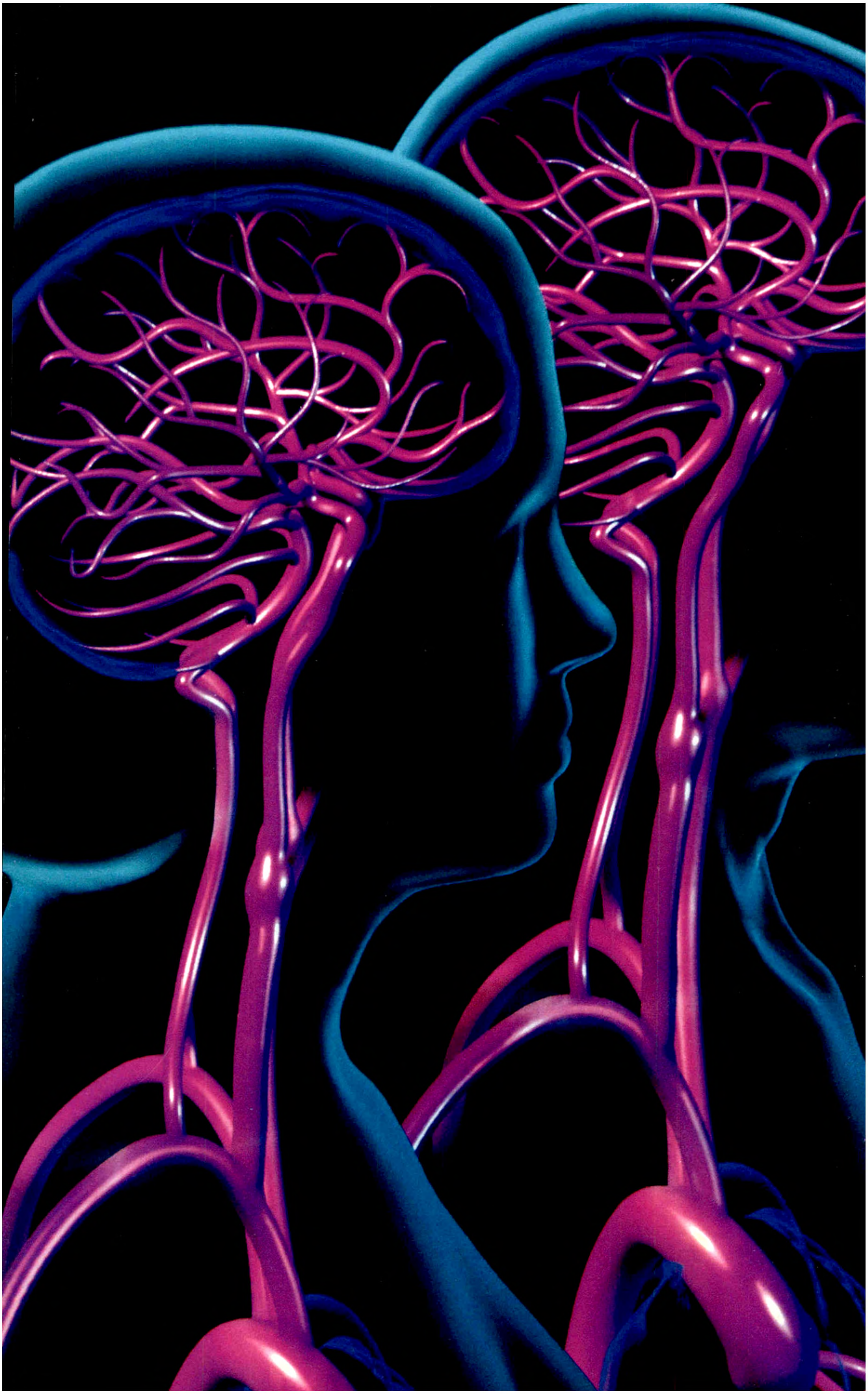

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*Analysis based on all study participants, which included patients with transient ischemic attack, transient monocular blindness, reversible ischemic neurological deficit, and minor stroke.

1. Hass WK, Easton JD, Adams HP Jr et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med.* 1989;321(8):501-507.
2. Gent M, Easton JD, Hachinski VC et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet.* 1989;1:1215-1220.
3. Biller J, Love BB, Gordon DL. Antithrombotic therapy for ischemic cerebrovascular disease. *Semin Neurol.* 1991;11:353-367.
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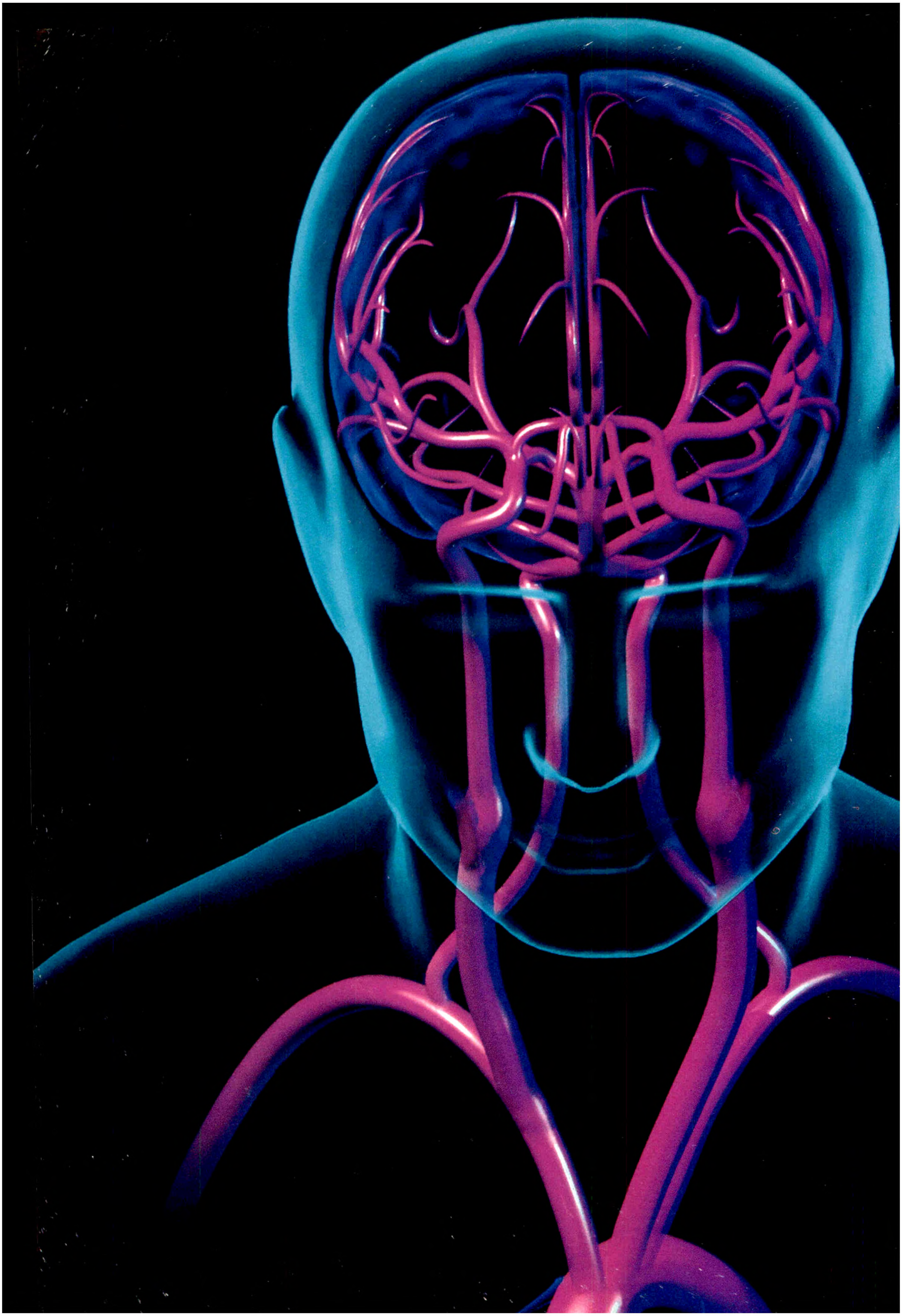

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- Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life threatening (see Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke
- Neutropenia[*] occurred in a total of 2.4% of patients (0.8% severe[†])
- The onset of severe neutropenia occurred 3 weeks to 3 months after the start of therapy, and was not typically associated with clinical signs or symptoms
- After the first 90 days, incidence of neutropenia was comparable to control, and was mild to moderate in nature
- CBC monitoring (including differentials) for neutropenia is therefore essential every 2 weeks for the first 3 months of therapy[‡]
- In clinical trials, all cases resolved 1 to 3 weeks after discontinuing therapy[§]
- Overall incidence of discontinuation for neutropenia: 1.3%

Other Side Effects

- Most frequent were diarrhea (12.5%), nausea (7.0%), dyspepsia (7.0%), and rash (5.1%)
- Most occurred early in therapy, although new onset of side effects can occur after several months
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- There was an 8%-10% average increase of serum cholesterol after 1 to 4 months of therapy with TICLID. Lipid subfraction ratios, however, remained unchanged.

[*] Defined as < 1200 neutrophils/mm^3, seen in 50 of 2048 patients. [†] Defined as < 450 neutrophils/mm^3, seen in 17 of 2048 patients.

[‡] More frequent monitoring is necessary for patients whose ANC have been consistently declining or are 30% less than the baseline count. After the first 3 months, CBCs need only be repeated for signs or symptoms suggestive of neutropenia. See Warnings section in full prescribing information. [§] With neutrophil levels returning to > 1200/mm^3.

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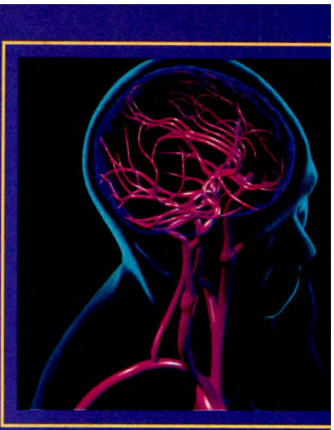
Ticlopidine HCl 250mg Tablets bid

SYNTEX



NEW **Ticlid**®

Ticlopidine HCl 250mg Tablets bid

Introducing the First Prescription Antiplatelet Agent that Significantly Reduces the Risk of Stroke

For further information, including the CBC Monitoring Program for TICLID, please call 1-800-TICLID-1.

TICLID®(ticlopidine hydrochloride) 250 mg Tablets

INDICATIONS AND USAGE TICLID is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life-threatening (See Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke. **CONTRAINDICATIONS** The use of TICLID® is contraindicated in the following conditions: Hypersensitivity to the drug. Presence of hematopoietic disorders such as neutropenia and thrombocytopenia. Presence of a hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding). Patients with severe liver impairment.

WARNINGS

Neutropenia

Neutropenia defined in these studies as an ANC <1200 neutrophils/mm^3 occurred in 50 of 2,048 (2.4%) stroke patients who received TICLID in clinical trials. *Severe Neutropenia (<450 neutrophils/mm^3):* Severe neutropenia and/or agranulocytosis occurred in 17 of the 2,048 (0.8%) patients who received TICLID. When the drug was discontinued in these patients, the neutrophil counts returned to normal (>1200 neutrophils/mm^3) within 1-3 weeks. *Mild to Moderate Neutropenia (451-1200 neutrophils/mm^3):* Mild to moderate neutropenia occurred in 33 of the 2,048 (1.6%) patients who received TICLID. Eleven of the patients discontinued treatment and recovered within a few days. In the remaining 22 patients, the neutropenia was transient and did not require discontinuation of therapy. The onset of severe neutropenia occurred 3 weeks to 3 months after the start of therapy with TICLID, with no documented cases of severe neutropenia beyond that time in the large controlled trials. The bone marrow typically showed a reduction in myeloid precursors. It is therefore essential that CBCs and white cell differentials be performed every two weeks starting from the second week to the end of the third month of therapy with TICLID, but more frequent monitoring is necessary for patients whose absolute neutrophil counts have been consistently declining or are 30% less than the baseline count. Neutropenia (an absolute neutrophil count (ANC) of less than 1200 neutrophils/mm^3) is calculated as follows: ANC = WBC × % neutrophils. If clinical evaluation and repeat laboratory testing confirm the presence of neutropenia (<1200/mm^3), the drug should be discontinued. In clinical trials, when therapy was discontinued immediately upon detection of neutropenia, the neutrophil counts returned to normal within 1-3 weeks. After the first three months of therapy, CBCs need be obtained only for patients with signs or symptoms suggestive of infection.

Thrombocytopenia Rarely, thrombocytopenia may occur in isolation or together with neutropenia. If clinical evaluation and repeat laboratory testing confirm the presence of thrombocytopenia (<80,000 cells/mm^3), the drug should be discontinued. Cholesterol Elevation TICLID® therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8-10% within one month of therapy and persist at that level. The ratios of the lipoprotein subfractions are unchanged. **Other Hematological Effects** Rare cases of pancytopenia and thrombotic thrombocytopenic purpura, some of which have been fatal, have been reported in Post-Marketing Surveillance. **Anticoagulant Drugs** The tolerance and safety of coadministration of TICLID with heparin, oral anticoagulants, or fibrinolytic agents has not been established. If a patient is switched from an anticoagulant or fibrinolytic drug to TICLID, the former drug should be discontinued prior to TICLID administration. **PRECAUTIONS General** TICLID should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or pathological conditions. If it is desired to eliminate the antiplatelet effects of TICLID prior to elective surgery, the drug should be discontinued 10-14 days prior to surgery. Several controlled clinical studies have found increased surgical blood loss in patients undergoing surgery during treatment with ticlopidine. In TASS and CATS it was recommended that patients have ticlopidine discontinued prior to elective surgery. Several hundred patients underwent surgery during the trials, and no excessive surgical bleeding was reported. Prolonged bleeding time is normalized within two hours after administration of 20 mg methylprednisolone i.v. Platelet transfusions may also be used to reverse the effect of TICLID on bleeding. **GI Bleeding** TICLID prolongs template bleeding time. The drug should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients on TICLID. (See Contraindications.) **Use in Hepatically Impaired Patients** Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of TICLID is not recommended in this population. (See Clinical Pharmacology and Contraindications.) **Use in Renally Impaired Patients** There is limited experience in patients with renal impairment. In controlled clinical trials, no unexpected problems have been encountered in patients having mild renal impairment and there is no experience with dosage adjustment in patients with greater degrees of renal impairment. Nevertheless, for renally impaired patients it may be necessary to reduce the dosage of ticlopidine or discontinue it altogether, if hemorrhagic or hematopoietic problems are encountered. (See Clinical Pharmacology) **Information for the Patient (See PPI)** Patients should be told that a decrease in the number of white blood cells (neutropenia) can occur with TICLID®, especially during the first three months of treatment, and that if neutropenia is severe, it could result in an increased risk of infection. They should be told it is critically important to obtain the scheduled blood tests to detect neutropenia. Patients should also be reminded to contact their physicians if they experience any indication of infection such as fever, chills, and sore throat, all of which may be consequences of neutropenia. All patients should be told that it may take them longer than usual to stop bleeding when they take TICLID and that they should report any unusual bleeding to their physician. Patients should tell physicians and dentists that they are taking TICLID before any surgery is scheduled and before any new drug is prescribed. Patients should be told to report promptly side effects of TICLID such as severe or persistent diarrhea, skin rashes, or subcutaneous bleeding, or any signs of cholestasis, such as yellow skin or sclera, dark urine, or light colored stools. Patients should be told to take TICLID with food or just after eating in order to minimize gastrointestinal discomfort. **Laboratory Tests** *Liver Function:* TICLID therapy has been associated with elevations of alkaline phosphatase and transaminases which generally occurred within 1-4 months of therapy initiation. In controlled clinical trials, the incidence of elevated alkaline phosphatase (greater than 2 times upper limit of normal) was 7.6% in ticlopidine patients, 6.0% in placebo patients and 2.5% in aspirin patients. The incidence of elevated AST (SGOT) (greater than 2 times upper limit of normal) was 3.1% in ticlopidine patients, 4.0% in placebo patients and 2.1% in aspirin patients. No progressive increases were observed in closely monitored clinical trials (e.g. no transaminase greater than 10 times the upper limit of normal was seen), but most patients with these abnormalities had therapy discontinued. Occasionally patients had developed minor elevations in bilirubin. Based on post-marketing and clinical trials experiences, liver function testing should be considered whenever liver dysfunction is suspected, particularly during the first four months of treatment. **Drug Interactions** Therapeutic doses of TICLID caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios, or being given to patients with hepatic impairment, may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine. Studies of specific drug interactions yielded the following results: ***Aspirin:*** Aspirin did not modify the ticlopidine-mediated inhibition of ADP-induced platelet aggregation, but ticlopidine potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of this combination has not been established and concomitant use of aspirin and ticlopidine is not recommended. (See Precautions – GI Bleeding). ***Antacids:*** Administration of TICLID after antacids resulted in an 18% decrease in plasma levels of ticlopidine. ***Cimetidine:*** Chronic administration of cimetidine reduced the clearance of a single dose of TICLID by 50%. ***Digoxin:*** Co-administration of TICLID with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected. ***Theophylline:*** In normal volunteers, concomitant administration of TICLID resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hr and a comparable reduction in total plasma clearance of theophylline. ***Phenobarbital:*** In six normal volunteers, the inhibitory effects of TICLID on platelet aggregation were not altered by chronic administration of phenobarbital. ***Phenytoin:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID and it may be useful to remeasure phenytoin blood concentrations. ***Propranolol:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID.

℞ ______

Ticlid
250 mg #30
Sig: 1 tab bid
with meals

Other Concomitant Therapy: Although specific interaction studie performed, in clinical studies, TICLID was used concomitantly blockers, calcium channel blockers, diuretics, and nonstero inflammatory drugs without evidence of clinically significan interactions. (See Precautions.) **Food Interaction:** The oral bioav ticlopidine is increased by 20% when taken after a meal. Admini TICLID with food is recommended to maximize gastrointestinal tol controlled trials, TICLID was taken with meals. **Carcino Mutagenesis, Impairment of Fertility** In a two-year oral carcinogen in rats, ticlopidine at daily doses of up to 100 mg/kg (610 mg/m tumorigenic. For a 70 kg person (1.73m^2 body surface area), represents 14 times the recommended clinical dose on a mg/kg b times the clinical dose on body surface area basis. In a 78 carcinogenicity study in mice ticlopidine at daily doses up to 275 m mg/m^2) was not tumorigenic. The dose represents 40 times the rec clinical dose on a mg/kg basis and 4 times the clinical dose on bo area basis. Ticlopidine was not mutagenic in *in vitro* Ames test, rat DNA-repair assay, and Chinese hamster fibroblast chromosomal test and *in vivo* mouse spermatozoid morphology test, Chines micronucleus test and Chinese hamster bone marrow cell sister chromatid exchange test. Ticlopidine was found effect on fertility of male and female rats at oral doses up to 400 mg/kg/day. **Pregnancy: Teratogenic Effects** Category B. Teratology studies have been conducted in mice (doses up to 200 mg/kg/day), rats (do 400 mg/kg/day) and rabbits (doses up to 200 mg/kg/day). Doses of 400 mg/kg in rats, 200 mg/kg/day in mice mg/kg in rabbits produced maternal toxicity as well as fetal toxicity, but there was no evidence of a teratogenic ticlopidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal re studies are not always predictive of a human response, this drug should be used during pregnancy only if clear **Nursing Mothers** Studies in rats have shown ticlopidine is excreted in the milk. It is not known whether th excreted in human milk. Because many drugs are excreted in human milk and because of the potential for seriou reactions in nursing infants from ticlopidine, a decision should be made whether to discontinue nursing or to disco drug, taking into account the importance of the drug to the mother. **Pediatric Use** Safety and efficacy in patients age of 18 have not been established. **Geriatric Use** Clearance of ticlopidine is somewhat lower in elderly pa trough levels are increased. The major clinical trials with TICLID were conducted in an elderly population with a age of 64 years. Of the total number of patients in the therapeutic trials, 45% of patients were over 65 years old were over 75 years old. No overall differences in effectiveness or safety were observed between these pa younger patients, and other reported clinical experience has not identified differences in responses between the e younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTION** reactions were relatively frequent, with over 50% of patients reporting at least one. Most (30 to 40%) inv gastrointestinal tract. Most adverse effects are mild, but 21% of patients discontinued therapy because of an adve principally diarrhea, rash, nausea, vomiting, G.I. pain, and neutropenia. Most adverse effects occur early in the treatment, but a new onset of adverse effects can occur after several months. The incidence rates of adverse even the following table were derived from multicenter, controlled clinical trials described above comparing TICLID, pla aspirin over study periods of up to 5.8 years. Adverse events considered by the investigator to be probably dr that occurred in at least one percent of patients treated with TICLID are shown in the following table:

Percent of Patients with Adverse Events in Controlled Studies

Event	TICLID (n = 2048) Incidence	Aspirin (n = 1527) Incidence	Placebo (n = 536) Incidence
Any Events	*60.0 (20.9)*	*53.2 (14.5)*	*34.3 (6.1)*
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	1.7 (0.9)
Dyspepsia	7.0 (1.1)	9.0 (2.0)	0.9 (0.2)
Rash	5.1 (3.4)	1.5 (0.8)	0.6 (0.9)
GI Pain	3.7 (1.9)	5.6 (2.7)	1.3 (0.4)
Neutropenia	2.4 (1.3)	0.8 (0.1)	1.1 (0.4)
Purpura	2.2 (0.2)	1.6 (0.1)	0.0 (0.0)
Vomiting	1.9 (1.4)	1.4 (0.9)	0.9 (0.4)
Flatulence	1.5 (0.1)	1.4 (0.3)	0.0 (0.0)
Pruritus	1.3 (0.8)	0.3 (0.1)	0.0 (0.0)
Dizziness	1.1 (0.4)	0.5 (0.4)	0.0 (0.0)
Anorexia	1.0 (0.4)	0.5 (0.3)	0.0 (0.0)
Abnormal Liver Function test	1.0 (0.7)	0.3 (0.3)	0.0 (0.0)

Incidence of discontinuation, regardless of relationship therapy, is shown in parentheses

Neutropenia/Thrombocytopenia See Warnings. **Gastrointestinal** TICLID therapy has been associated with a gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild, but about 13% discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and ty resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy discontinued. **Hemorrhagic** TICLID has been associated with a number of bleeding complications such as ec epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding and perioperative bleeding. Intracerebra was rare in clinical trials with TICLID, with an incidence no greater than that seen with comparator agents. (0.5%, aspirin 0.6%, placebo 0.75%.) **Rash** Ticlopidine has been associated with a maculopapular or urticarial with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean onset time of 11 days. discontinued, recovery occurs within several days. Many rashes do not recur on drug rechallenge. There have reports of severe rashes. **Less Frequent Adverse Reactions (Probably Related)** Clinical adverse experiences in 0.5 to 1.0 percent of patients in the controlled trials include: Digestive System: GI fullness. Skin and Ap urticaria. Nervous System: headache. Body as a Whole: asthenia, pain. Hemostatic System: epistaxis. Speci tinnitus. In addition, rarer, relatively serious events have also been reported, mainly from foreign post experience: Pancytopenia, hemolytic anemia with reticulocytosis, allergic pneumonitis, systemic lupus (posi peripheral neuropathy, vasculitis, serum sickness,arthropathy, hepatitis, cholestatic jaundice, nephrotic syndrome hyponatremia, immune thrombocytopenia and thrombocytopenic thrombotic purpura (TTP). **OVERDOSAGE** O deliberate overdosage with TICLID has been reported by foreign postmarketing surveillance program. A 38 yea took a single 6000 mg dose of TICLID (equivalent to 24 standard 250 mg tablets). The only abnormalities rep increased bleeding time and increased SGPT. No special therapy was instituted and the patient recover sequelae. Single oral doses of ticlopidine at 1600 mg/kg and 500 mg/kg were lethal to rats and mice, re Symptoms of acute toxicity were GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and gait. **DOSAGE AND ADMINISTRATION** The recommended dose of TICLID is 250 mg BID taken with food. O have not been studied in controlled trials for these indications.

SYNTEX

SYNTEX LABORATORIES, INC.
PALO ALTO, CA 94304

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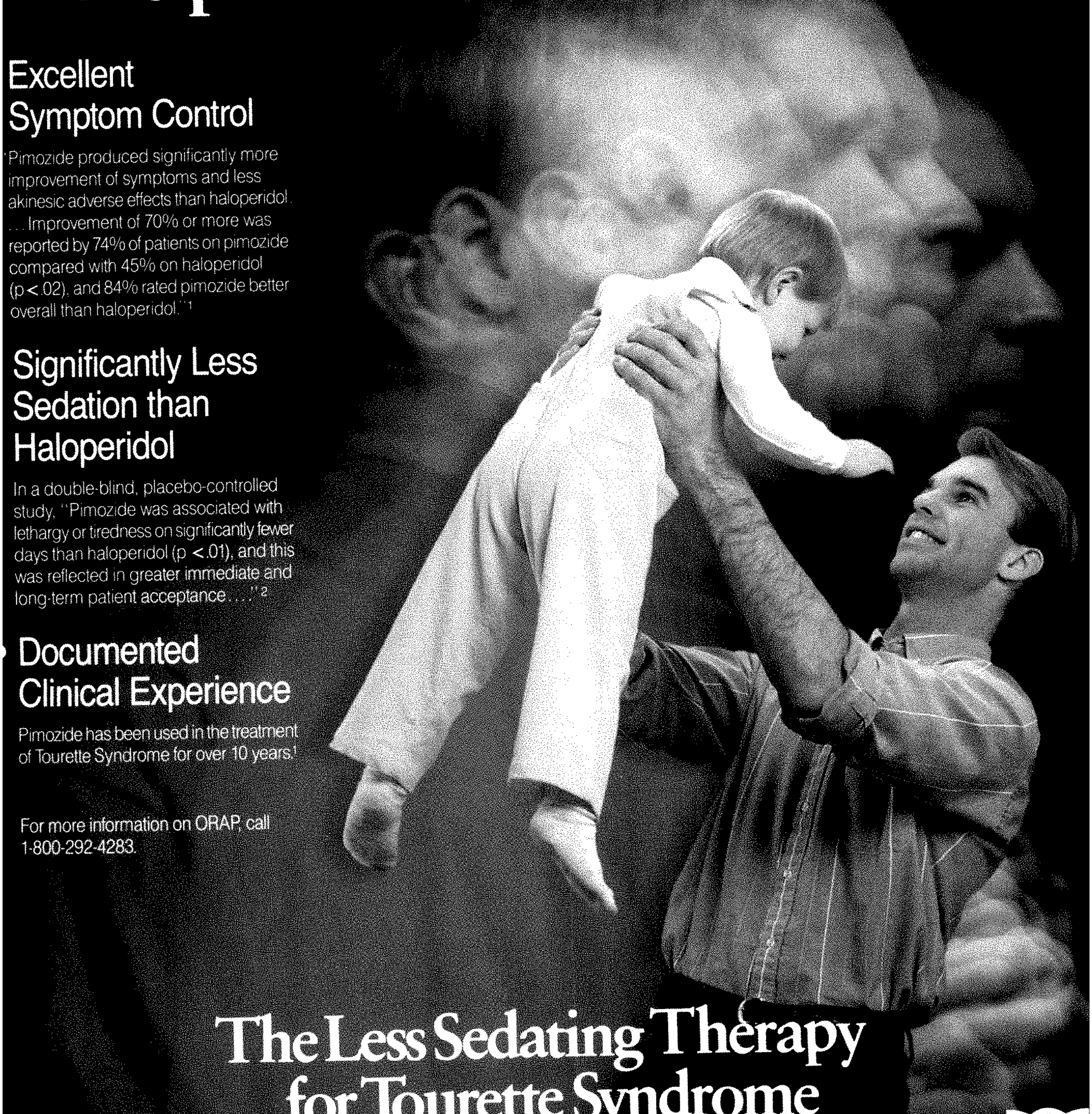
Printed in U.S.A.

In Tourette Syndrome

ORAP™

(pimozide) Tablets

Helps Patients Be Themselves*



Excellent Symptom Control

"Pimozide produced significantly more improvement of symptoms and less akinesic adverse effects than haloperidol. . . . Improvement of 70% or more was reported by 74% of patients on pimozide compared with 45% on haloperidol ($p < .02$), and 84% rated pimozide better overall than haloperidol."[1]

Significantly Less Sedation than Haloperidol

In a double-blind, placebo-controlled study, "Pimozide was associated with lethargy or tiredness on significantly fewer days than haloperidol ($p < .01$), and this was reflected in greater immediate and long-term patient acceptance . . ."[2]

Documented Clinical Experience

Pimozide has been used in the treatment of Tourette Syndrome for over 10 years.[1]

For more information on ORAP, call 1-800-292-4283.

The Less Sedating Therapy for Tourette Syndrome

* ORAP is indicated for patients who have failed to respond satisfactorily to standard treatment.

Please see following page for a brief summary of prescribing information.

GATE Pharmaceuticals
Division of Lemmon Company

GATE

ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS–Information for Patients).

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS–Information for Patients.)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS–Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such as phenothiaznes, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks

Labor and Delivery This drug has no recognized use in labor or delivery.

Nursing Mothers It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder

ADVERSE REACTIONS

General Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia: Hyperpyrexia has been reported with other antipsychotic drugs.

Clinical Trials The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Diso limited, uncommon adverse reactions may not have been detected. The ph should consider that other adverse reactions associated with antipsychotics may c

Other Adverse Reactions In addition to the adverse reactions listed above, thos below have been reported in U.S. clinical trials of ORAP in conditions oth Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema

Cardiovascular/Respiratory: Postural hypotension, hypotension, hypert tachycardia, palpitations

Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress

Endocrine: Loss of libido

Metabolic/Nutritional: Weight gain, weight loss

Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia

Psychiatric: Excitement

Skin: Rash, sweating, skin irritation

Special Senses: Blurred vision, cataracts

Urogenital: Nocturia, urinary frequency

Postmarketing Reports The following experiences were described in spont postmarketing reports. These reports do not provide sufficient information to est clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) wo an exaggeration of known pharmacologic effects and adverse reactions, th prominent of which would be: 1) electrocardiographic abnormalities, 2) extrapyramidal reactions, 3) hypotension, 4) a comatose state with resp depression.

In the event of overdosage, gastric lavage, establishment of a patent airway necessary mechanically-assisted respiration are advised. Electrocardiog monitoring should commence immediately and continue until the ECG paramet within the normal range. Hypotension and circulatory collapse may be countera use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agen as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be u case of severe extrapyramidal reactions, antiparkinson medication sho administered. Because of the long half-life of pimozide, patients who take an o should be observed for at least 4 days. As with all drugs, the physician should c contacting a poison control center for additional information on the treatm overdose.

DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifes in Tourette's Disorder patients below the age of twelve are not available. Conse the suppression of tics by ORAP requires a slow and gradual introduction of th The patient's dose should be carefully adjusted to a point where the suppression and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially dur period of dose adjustment (see WARNINGS and PRECAUTIONS–Laboratory Tests

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a divided doses. The dose may be increased thereafter every other day. Most patie maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whe not tics persist at the level and extent first identified. In attempts to reduce the do ORAP, consideration should be given to the possibility that increases of tic intens frequency may represent a transient, withdrawal related phenomenon rather than a of disease symptoms. Specifically, one to two weeks should be allowed to elapse one concludes that an increase in tic manifestations is a function of the und disease syndrome rather than a response to drug withdrawal. A gradual withdr recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP-2" 57844-187-01, bottles of 100.

Dispense in tight, light-resistant containers as defined in the official compendium

Made in Canada

Manufactured by:
McNeil Pharmaceutical, (Canada) Ltd.
Stouffville, Ontario L4A 7x7

Printed
Rev

GATE Pharmaceuticals
Division of Lemmon Company

1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

Calendar of Meetings

May

13 "Update on Diagnosis and Treatment of Headaches," Cleveland (Ohio) Clinic Foundation. Contact Department of Continuing Education, The Cleveland Clinic Educational Foundation, 9500 Euclid Ave, Room TT-31, Cleveland, OH 44195-5241; (216) 444-5696; (800) 762-8173.

June

16-20 Third International Cleveland (Ohio) Clinic–Bethel Epilepsy Symposium, Cleveland. Contact Nancy Robbins, The Cleveland Clinic Foundation, Desk S-90, 9500 Euclid Ave, Cleveland, OH 44195-5226.

25-27 Second European Stroke Conference, Lausanne, Switzerland. Contact A. Steck, Service de Neurologie, CHUV, CH-1011 Lausanne, Switzerland.

26-27 International Symposium on Neurofibromatosis, Vienna, Austria. Contact Elizabeth Ribar-Maurer, Wiener Medizinische Akademie, Alserstrasse 4, A-1090 Wien, Austria.

27-July 1 Third Meeting of the European Neurological Society, Lausanne, Switzerland. Contact Congress Secretariat, European Neurological Society 1992, c/o AKM Congress Service, Clarastrasse 57, CH-4005 Basel, Switzerland.

July

13-17 Annual Diagnostic Imaging Seminar, Edgartown, Mass. Contact Nancy Fedullo, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104; (215) 662-6904.

14-17 Fourth International Conference on Neuroscience of Human Immunodeficiency Virus Infection, Amsterdam, the Netherlands. Contact Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, the Netherlands.

20-22 "Neurological Encounters: 1492-1992," Tenerife, Canary Islands, Spain. Contact Alberto Portera-Sanchez, Hospital "12 de Octubre," Ctra de Andalucia, Km 5, 400, 28041 Madrid, Spain.

August

4-9 "Neuropsychiatric Aspects of Politics and Politicians," Mauna Kea Beach Hotel, Kamuela, Hawaii. Contact Ann McCormick, Southern California Neuropsychiatric Institute, 6794 La Jolla Blvd, La Jolla, CA 92037; (619) 454-2102.

LETTERS TO THE EDITOR

Progressive Nemaline (Rod) Myopathy as a Presentation of Human Immunodeficiency Virus Infection

To the Editor.—Nemaline (rod) myopathy associated with human immunodeficiency virus (HIV) infection has been reported in male patients at risk for the infection.[1,2]

Report of a Case.—We report the case of a 23-year-old woman who presented with a 6-month history of progressive weakness. Neuromuscular examination showed marked proximal muscle weakness and an exaggerated lordotic posture. An electromyogram was mildly abnormal, the serum creatine kinase concentration was borderline elevated, metabolic study results were normal, and family history was negative. A deltoid muscle biopsy specimen revealed prominent random atrophic myofibers containing numerous intracytoplasmic rod bodies, especially in type 1 fibers. No inflammatory response was present. Electron microscopy revealed the bodies to be electron-dense filamentous accumulations that had a crystalline periodicity on cross-section characteristic of nemaline rods. No viral particles were noted. A serum HIV titer drawn at the time of the biopsy was positive by enzyme-linked immunosorbent assay and Western blot analysis. The patient denied use of intravenous drugs or exposure to HIV. Treatment with intravenous methylprednisolone followed by prednisone, 40 mg daily, resulted in marked improvement in strength after 6 months. The patient has shown no signs or symptoms of acquired immunodeficiency syndrome or acquired immunodeficiency syndrome–related complex, and a repeated HIV titer remains positive.

Comment.—This case suggests that patients with no risk factors for HIV or symptoms of acquired immunodeficiency syndrome may present with a progressive rod myopathy as the initial sign. Response to prednisone therapy suggests an autoimmune mechanism for the myopathy. It is possible that some of the reported cases of late-onset rod myopathy may be autoimmune in origin.

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1. Gonzales MF, Olney RK, So YT, et al. Subacute structural myopathy associated with human immunodeficiency virus infection. *Arch Neurol.* 1988;45:585-587.

2. Simpson DM, Bender AN. Human immunodeficiency virus-associated myopathy: analysis of 11 patients. *Ann Neurol.* 1988;24:79-84.

Neurosyphilis and Human Immunodeficiency Virus Type 2 Infection

To the Editor.—In a recent study designed to know the prevalence of neurosyphilis in immunodeficiency virus type 1 infection (HIV-1)–seropositive persons, Berger[1] found a significant rate of unexpected neurosyphilis compared with HIV-1–negative patients. He also detected a high association (46%) of reactive serum syphilitic test results and HIV-positive patients. In our Dermatology Department in a General Hospital in Barcelona, Spain, from January 1, 1990, through October 1, 1991, we observed that 14 (40%) of 35 patients with syphilis also had HIV infection. Nine of them were seropositive to HIV-1, and the remaining five were seropositive to HIV-2. Ten patients were black West African immigrants, and four were white local residents. All but three were men, aged from 20 to 36 years. The average time living in Spain in the immigrant group was 4.6 years. The only risk factor for HIV infection among African patients was heterosexual intercourse with prostitutes. Three white patients were parenteral drug users, and the other was homosexual. Cerebrospinal fluid examination was carried out in six of 14 patients with syphilis and HIV infection. One of them suffered from symptomatic neurosyphilis despite the treatment with 7.2 megaunits of benzathine-penicillin for a secondary syphilis 1.5 years earlier. This patient was a black man seropositive to HIV-2. The neurologic symptoms improved with intravenous crystalline penicillin G, 4 megaunits every 4 hours for 14 days. Neurologic symptoms were absent in the other five patients, and the cerebrospinal fluid VDRL test revealed negative results. However, three of these patients had more than 5 lymphocytes per cubic milliliter and increased protein levels, and for this reason they were treated with intramuscular procaine penicillin, 2.4 megaunits daily for 2 weeks.

Based on these findings, we would like to emphasize (1) the high incidence of association between syphilis and HIV infection, which is similar to that reported by Berger; (2) the possibility that neurosyphilis may be encountered in HIV-2–seropositive-patients; and (3) the convenience of higher and more prolonged doses of penicillin in HIV-seropositive patients affected by syphilis.

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1. Berger JR. Neurosyphilis in human immunodeficiency virus type 1–seropositive individuals. *Arch Neurol.* 1991;48:700-702.

Violence: Resensitizing the Inured

To the Editor.—The editorial by Menken,[1] inviting readers of the Archives to contribute to a forthcoming issue on violence, provided an inadvertent insight concerning that topic. Menken referred to an article[2] in a British journal. The reference, as printed in the ARCHIVES, contained two typographical errors, making the title of the article "The Treatment of the Multiple Inured Patient in the United Kingdom."

Sometimes a typo is just a typo, but "inured" makes a trenchant comment on societies in which violence has become highly prevalent (here in the United States even more than in the United Kingdom): it is likely that there are, indeed, many (if not "multiple") patients who, before they themselves became surviving victims of violence, had been inured to violence.

The forthcoming publications by the journals of the American Medical Association may help to resensitize us readers to problems we have, regrettably, become quite accustomed to reading about. I hope so. Violence is something that no segment of society can afford to get used to.

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1. Menken M. Violence. *Arch Neurol.* 1991; 48:1121.
2. Court-Brown CM. The treatment of the multiply injured patient in the United Kingdom. *J Bone Joint Surg Br.* 1990;72:345-346.

Breathing Is Controlled Independently by Voluntary, Emotional, and Metabolically Related Pathways

To the Editor.—Munschauer et al[1] describe an interesting example of a man with a magnetic resonance image that demonstrated paramedian ventral pontine damage. He breathed normally at rest and in response to carbon dioxide stimulation, but he was unable to initiate either breathing or swallowing by voluntary effort. Recent, indirect, physiologic studies employing functional activation of cerebral blood flow[2] indicate that at least the diaphragm enjoys direct representation in the cerebral motor cortex, premotor cortex, supplementary motor area, and cerebellum. The results of transcranial magnetic stimulation[3] confirm the finding and suggest that considerable lateralization exists in cerebral diaphragmatic control since unilateral stimulation over motor-premotor cortex from either hemisphere evokes predominantly contralateral diaphragmatic movement in a manner similar to that observed with voluntary acts of the limbs. Evidently, this higher, cerebral regulation of respiratory striated muscle subserves the major behavioral functions of the system.

Munschauer et al, reasoning from their patient's lesion found on magnetic resonance imaging, suggest that the voluntary breathing pathway descends from the cerebrum to the lower bulbospinal level via corticospinal pathways lying in the paramedian basis pontis. Postmortem evidence published in an earlier study[4] (Fig 1) supports this suggestion. The cited figure shows a small paramedian infarct in the basis pontis of a man who before death retained voluntary movement of the extremities but who, nevertheless, had lost all capacity either to breathe or swallow voluntarily. Indeed, when he was urged to breathe during the apneic phase of periodic (Cheyne-Stokes) breathing, he threw up his hands to express the futility of his efforts.

Figure 4 in reference 4 also indicates that even large lesions of the rostral pontine base, approaching total transection of that structure, do not seriously disturb rhythmic, physiologically effective, human breathing unless the injury also damages the respiratory feedback circuits that lie in the rostral pontine tegmentum. It will be remembered from standard textbook sources that both experimental and patient studies have demonstrated repeatedly that, after rostral brain-stem transection, lower pontine-medullary centers continue to drive the respiratory muscles in their efficient regulation of oxidative metabolism and systemic acid-base balance.

As noted earlier,[4] breathing is the only coordinated skeletal muscle act that continuously fulfills and seamlessly integrates continuous metabolic and intermittent behavioral functions without normally disrupting the efficiency of either in the process. What Munschauer et al now have shown us is that at least two prepontine descending pathways must contribute to the bulbospinal regulation of breathing: one voluntary, the other emotional. Their finding of a patient who lost the first capacity but retained the second implies that limbic system outputs bypass corticospinal pathways that regulate voluntary breathing activity as they induce the respiratory components of pseudobulbar emotional expression.

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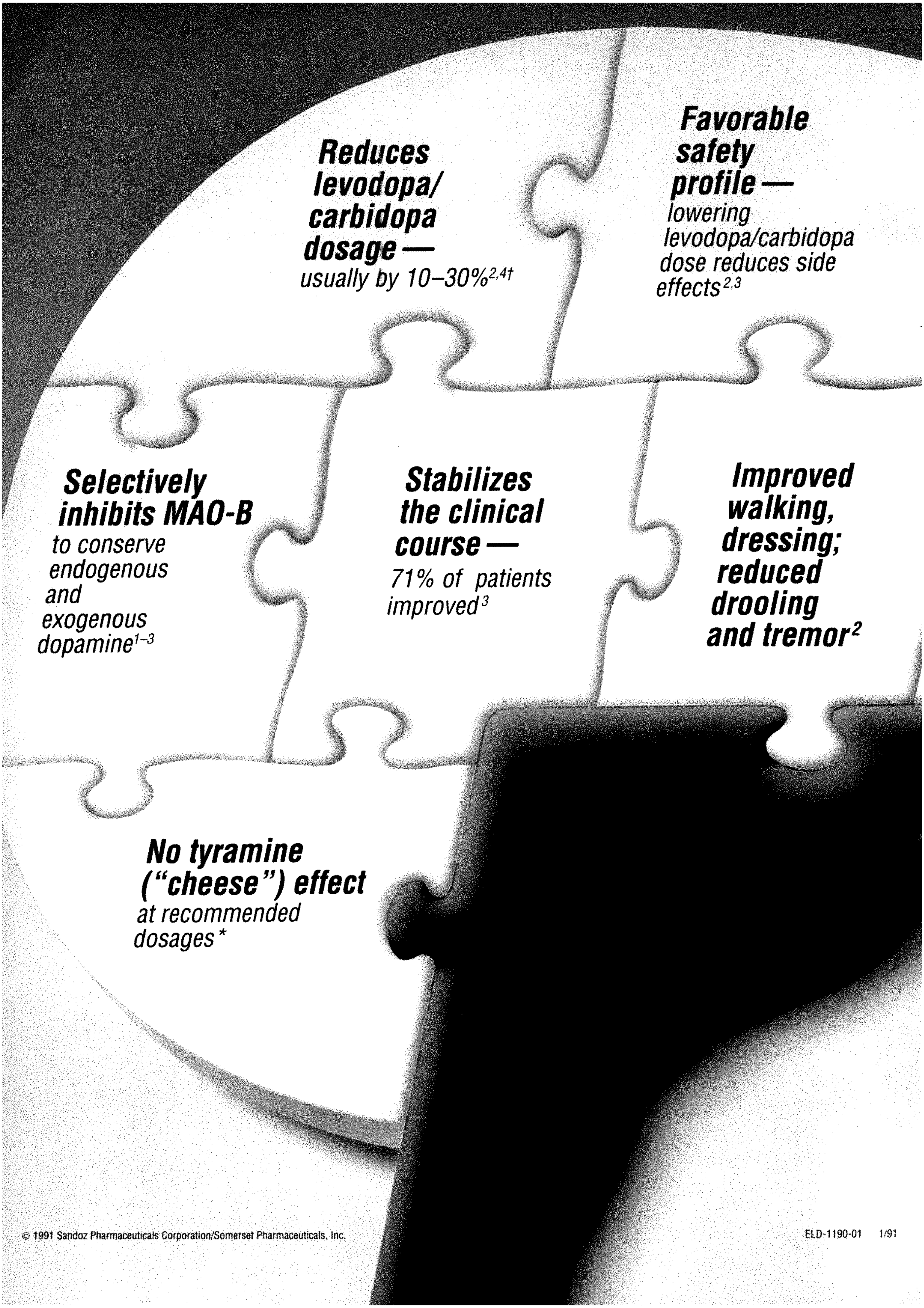
1. Munschauer FE, Mador MJ, Ahuja A, Jacobs L. Selective paralysis of voluntary but not limbically influenced automatic respiration. *Arch Neurol.* 1991;48:1190-1192.
2. Colebatch JG, Adams L, Murphy K, et al. Regional cerebral blood flow during volitional breathing in man. *J Physiol.* 1991;443:91-103.
3. Maskill D, Murphy K, Mier A, Owen M, Guz A. Motor cortical representation of the diaphragm in man. *J Physiol.* 1991;443:105-121.
4. Plum F. Neurological integration of behavioral and metabolic control of breathing. In: Porter R, ed. *Ciba Foundation Hering Breuer Centenary Symposium: Breathing.* London, England: J & A Churchill; 1970; 159-181.



Reduces levodopa/carbidopa dosage —
usually by 10–30%[2,4†]

Favorable safety profile —
lowering levodopa/carbidopa dose reduces side effects[2,3]

Selectively inhibits MAO-B
to conserve endogenous and exogenous dopamine[1–3]

Stabilizes the clinical course —
71% of patients improved[3]

Improved walking, dressing; reduced drooling and tremor[2]

No tyramine ("cheese") effect
*at recommended dosages**

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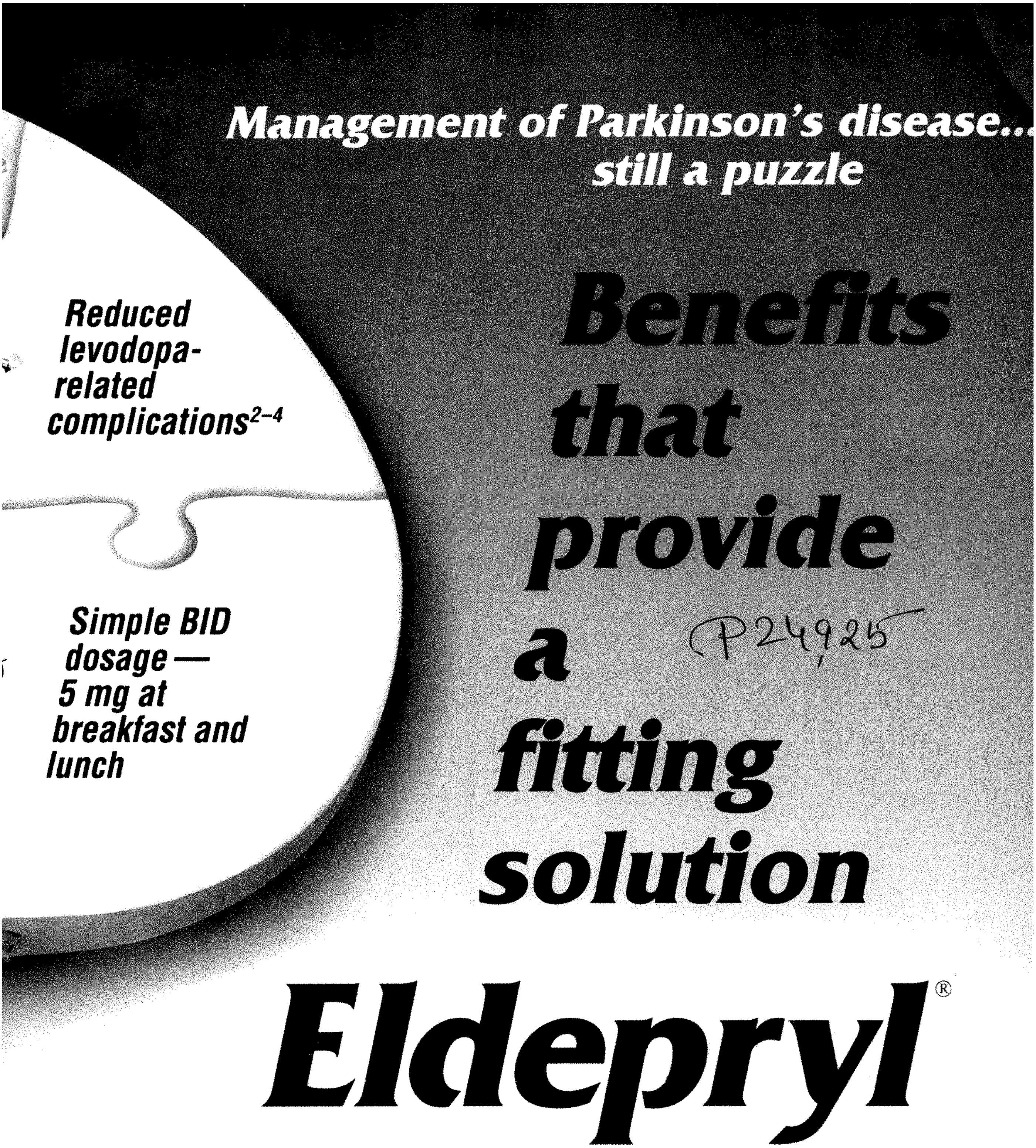
ELD-1190-01 1/91



Reduced levodopa-related complications[2–4]
Simple BID dosage — 5 mg at breakfast and lunch

Management of Parkinson's disease... still a puzzle

Benefits that provide a fitting solution

P24925

Eldepryl®

(SELEGILINE HYDROCHLORIDE)

Fits your therapeutic strategy

---

*Higher doses have not been shown to increase benefit and have increased the risk of side effects. Please see Dosage and Administration section of prescribing information.

† Further reduction of levodopa/carbidopa may be possible during continued selegiline therapy.

See next page for brief summary of prescribing information.

Eldepryl®

(SELEGILINE HYDROCHLORIDE)

BRIEF SUMMARY: Please see package insert for full prescribing information.

CLINICAL PHARMACOLOGY:

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

INDICATIONS AND USAGE:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is contraindicated in patients with a known hypersensitivity to this drug.

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is contraindicated for use with meperidine (DEMEROL and other trade names). This contraindication is often extended to other opioids (see Drug Interactions).

WARNINGS:

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Definitive clinical data on the concomitant use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) and fluoxetine hydrochloride (PROZAC) is not available. Death has been reported to occur following the initiation of therapy with nonselective MAOI's (NARDIL, PARNATE) shortly after discontinuation of fluoxetine. To date, this reaction has not been reported with ELDEPRYL® (SELEGILINE HYDROCHLORIDE), however, since the mechanism of this reaction is not fully understood it seems prudent, in general, to avoid this combination. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately 5 half-lives) should elapse between discontinuation of fluoxetine and initiation of MAOI therapy. Based on experience with the combined use of MAOI's and tricyclic antidepressants, at least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with fluoxetine.

PRECAUTIONS:

General: Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients: Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline have not been reported, documented experience is limited. Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests: No specific laboratory tests are deemed essential for the management of patients on ELDEPRYL® (SELEGILINE HYDROCHLORIDE). Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions: The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in a man receiving selegiline and meperidine, as well as other medications. Symptoms resolved over days when the combination was discontinued. This case is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination. While it cannot be said definitively that all of these reactions were caused by this combination, they are all compatible with this well recognized interaction. No other interactions attributed to the combined use of selegiline and other drugs have been reported. However, because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. (See WARNINGS and PRECAUTIONS.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies have not been performed to date to evaluate the carcinogenic potential of selegiline hydrochloride.

Pregnancy: *Pregnancy Category C.* Insufficient animal reproduction studies have been done with selegiline to conclude that selegiline poses no teratogenic risk. However, one rat study carried out at doses as much as 180 fold the recommended human dose revealed no evidence of a teratogenic effect. It is not known whether selegiline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Selegiline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use: The effects of selegiline hydrochloride in children have not been evaluated.

ADVERSE REACTIONS:

Introduction: The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have been also reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness and weight loss.

Experience with ELDEPRYL® (SELEGILINE HYDROCHLORIDE) obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

CENTRAL NERVOUS SYSTEM:

Motor/Coordination/Extrapyramidal: increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric: hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

AUTONOMIC NERVOUS SYSTEM: Dry mouth, blurred vision, sexual dysfunction.

CARDIOVASCULAR: Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

GASTROINTESTINAL: Nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

GENITOURINARY/GYNECOLOGIC/ENDOCRINE: Slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

SKIN AND APPENDAGES: Increased sweating, diaphoresis, facial hair, hair loss, hemotoma, rash, photosensitivity.

MISCELLANEOUS: Asthma, diplopia, shortness of breath, speech affected.

POSTMARKETING REPORTS: The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE).

CNS: Seizure in dialyzed chronic renal failure patient on concomitant medications.

*indicates events reported only at doses greater than 10 mg/day.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N = 49	placebo N = 50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

OVERDOSAGE:

Selegiline: No specific information is available about clinically significant overdoses with ELDEPRYL® (SELEGILINE HYDROCHLORIDE). However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g., tranylcypromine (PARNATE), isocarboxazide (MARPLAN), and phenelzine (NARDIL)].

Overdose with Non-Selective MAO Inhibition: NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions for Overdose

NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physician's Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

[Literature issued December, 1991 011-25-P-105]

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Special Article

Gerstmann's Syndrome

Arthur L. Benton, PhD

• Recent case reports describe the occurrence of a more or less pure Gerstmann syndrome in association with a focal lesion in the posterior perisylvian territory of the brain's left hemisphere. In addition, an electrocortical stimulation study reported the Gerstmann symptom combination and a number of other symptom combinations on stimulation of small areas in the left posterior parietotemporal cortex. The neuropsychological implications of these and other recent findings are considered in light of the variety of "syndromes" produced by lesions in this region, the rare occurrence of Gerstmann's syndrome, and its appearance as a consequence of lesions in diverse cerebral areas.

(*Arch Neurol.* 1992;49:445-447)

Three recently published case reports have described patients who exhibited a more or less pure Gerstmann syndrome resulting from lesions in the territory of the left angular and supramarginal gyri.[1-3] In addition, a cortical stimulation study of an epileptic patient reported by Morris and his coworkers[4] elicited the four components of the syndrome on stimulation of certain loci in the transition zone between the angular and supramarginal gyri. These contributions have important implications for our understanding of a long-standing controversial issue. They deserve comment, particularly from someone who, beginning some 40 years ago, has repeatedly questioned the reality and neuropsychological significance of the syndrome.[5-9]

The debate over Gerstmann's syndrome is well known. It centers on four questions: (1) whether the syndrome exists as a more or less autonomous combination unaccompanied by other behavioral indications of brain disease; (2) whether the combination has the specific neuroanatomic significance attributed to it by Gerstmann, ie, that it implies the presence of a focal lesion in the territory of the angular gyrus; (3) whether the syndrome has a special status compared with other combinations of deficits that are exhibited by patients with posterior perisylvian lesions of the left hemisphere[8,10]; and (4) whether the combination is the behavioral expression of a single underlying basic deficit (Grundstörung).

The empirical grounds for questioning the reality and neuropsychological significance of the syndrome may be briefly stated: (1) Until recently, a complete Gerstmann syndrome not accompanied by other defects, such as aphasic disorder, memory impairment, or constructional apraxia, had not been encountered, even in large series of cases.[8,10,11] (2) On the behavioral level, the associations between the components of the syndrome appeared to be no closer than the associations between the components and deficits lying outside the syndrome, a finding that cast doubt on the existence of an underlying Grundstörung.[8,9] (3) The neuroanatomic basis of a complete Gerstmann syndrome had been found to be extensive disease of the posterior left hemisphere rather than a lesion restricted to the angular gyrus.[10,11] (4) Bilateral finger agnosia, the nuclear component of the syndrome, had been found to be almost invariably associated with either dementia or aphasic disorder.[12] (5) The components of the syndrome represent broad categories, each of which includes a number of more specific deficits, eg, apractic vs aphasic agraphia, own body vs confronting person right-left orientation, and aphasic acalculia vs arithmetia. Investigators have differed in the ways in which they have defined these components; consequently, it is unclear exactly which deficits constitute the syndrome.[9]

REPORT OF CASES

The first case report is that of Roeltgen et al.[1] Their patient was a 64-year-old man who was examined 1 week after an ischemic cerebral infarction. He clearly showed all four Gerstmann deficits in the absence of aphasic disorder, general mental impairment, memory deficit, spatial disorientation, and visuoconstructional difficulties. Computed tomography (CT) performed 1 week after the episode disclosed a cortical lesion involving the upper part of the left angular and the supramarginal gyri. The authors correctly pointed out that their case represents the first instance of Gerstmann's syndrome resulting from a documented focal lesion in the territory of the angular and supramarginal gyri. They attributed the rarity of such cases to the fact that cerebral lesions are unlikely to be strictly limited to this territory.

Varney[2] also described an aggregation of Gerstmann deficits, the character of which changed with time. Shortly after the hospital admission of his patient, a 59-year-old man with a 12th grade education, because of progressive weakness of the right arm and leg and episodes of dizziness, a "CT scan indicated increased uptake in the upper left parietal region consistent with stroke." He was alert and cooperative, and, except for severe agraphia, showed no evidence of aphasic disorder. With the Arithmetic Reasoning and Digit Symbol subtests omitted, Wechsler's Adult Intelligence Scale Verbal and Performance IQ

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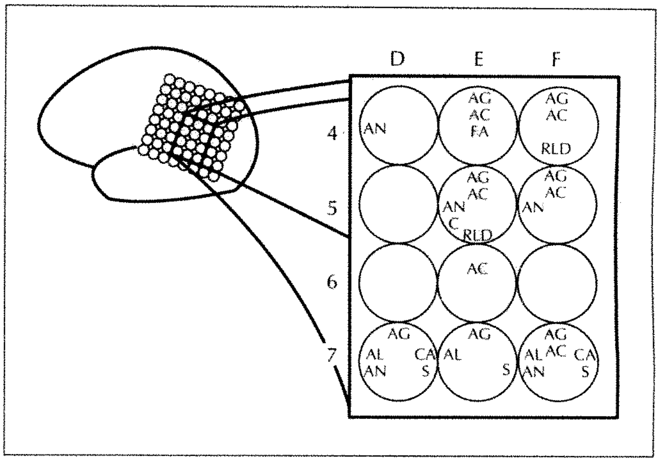
scores were 96 and 102, respectively, with a remarkably even performance pattern and age-corrected subtest scale scores ranging from 9 to 11. Within this context of intact verbal skills and intellectual functioning, the patient showed marked impairment in performance on all four Gerstmann tasks. At this time, the patient showed "a classic Gerstmann syndrome without aphasia or significant mental impairment." When he was seen for a second time 29 days after admission, after he had had a grand mal seizure and his motor weakness had progressed, the patient showed a severe nonfluent aphasia and a marked visuoconstructional disability. His Gerstmann performances were the same as those observed during the first examination. A CT scan indicated a lesion in the upper left high parietal region that was somewhat larger than that shown on the first scan. Thus, on this occasion he presented a "clear picture of a Gerstmann syndrome in association with aphasia and visuoconstructive deficits." The patient was seen for a third time 4 months after the second examination. He was still clearly aphasic but with some improvement in test performances. The pattern of Gerstmann performances was now uneven. While finger recognition and calculation remained impaired, right-left discrimination and writing had recovered to normal or near-normal levels. Varney concluded that, while a more or less pure Gerstmann syndrome unaccompanied by aphasia, dementia, or visuoconstructional disability can occur, the differential recovery of functions in his case argues against regarding the combination of symptoms as a coherent syndrome.

The final case report to be considered is that of Mazzoni et al,[3] whose patient sustained a penetrating head wound in the left parietal region, resulting in severe headache, right-sided sensory defect, and anomia. Neuropsychological examination 2 months after the accident, at which time the naming difficulty was no longer evident, disclosed that, with the exception of writing, performances on verbal and nonverbal tests were generally normal. The patient exhibited some poor performances on visuoconstructional and visual memory tests, but on reexamination 6 months later, he performed adequately on these tests. A CT scan obtained at this later date is described as "showing a cortical-subcortical hypodense area limited to the left angular gyrus region." (It is not possible to interpret with confidence the reduced and degraded reproduction of the scan presented in the report; the mapping of the scan in another figure suggests a considerably larger lesion involving the supramarginal gyrus and inferior parietal lobule as well as the angular gyrus.) Mazzoni et al concluded that their findings supported "the existence of a pure Gerstmann syndrome in the absence of any aphasic disorder, strictly linked to a lesion limited to the left angular gyrus."

The observations described in the cortical stimulation study of Morris et al[4] involving a 17-year-old epileptic boy may be considered in connection with these case reports. Repeated stimulation of different loci in the posterior perisylvian region through 3-mm-diameter electrodes during a period of 4 weeks elicited the diverse defects associated with disease in this region, ie, acalculia, agraphia, alexia, anomia, constructional apraxia, finger agnosia, and right-left disorientation (Figure). The patient showed none of these deficits under normal conditions. As shown in the Figure, stimulation of adjacent loci E4 and F4, located in the transition zone between the angular and supramarginal gyri, produced acalculia, agraphia, and finger agnosia in one locus and right-left disorientation in the other, the combination thus producing a complete Gerstmann syndrome without accompanying deficits, such as anomia, alexia, or constructional apraxia.

Inspection of the data in the Figure discloses a variety of symptom combinations that would be produced by stimulation at either a single locus or pairs of adjacent loci. Those symptom complexes that include two or more Gerstmann deficits (and to which I have assigned eponymic labels) are listed in the Table. The most extensive is De Renzi's syndrome, which is produced by stimulation at loci E4 through E5 and which includes all the Gerstmann deficits as well as anomia. This is the only aggregation that includes all four components of Gerstmann's syndrome. Stimulation at locus E5 or at loci F4 through F5 produces all the deficits, except finger agnosia (Heilman's syndrome). Poeck's syndrome, produced by stimulation at loci D4 through E4 or loci E4 through F5, consists of all deficits, except right-left disorientation. Stimulation at locus F7 produces two Gerstmann deficits (agraphia and acalculia) in combination with anomia and constructional apraxia (Vignolo's syndrome). As will be seen, still other "syndromes" can be derived from inspection of the Figure.



Deficits elicited by electrical stimulation at different loci in the posterior perisylvian region of the brain. AN indicates anomia; AG, agraphia; AC, acalculia; FA, finger agnosia; RL, right-left disorientation; C, conversation difficulty; AL, alexia; S, spelling errors; and CA, constructional apraxia. (From Morris et al.[4])

Syndromes Elicited by Stimulation to the Left Posterior Perisylvian Cortex*

Syndrome	Components†	Locus‡
Gerstmann's	AC, AG, FA, RLD	E4-F4
De Renzi's	AC, AG, AN, FA, RLD	E4-E5
Heilman's	AC, AG, AN, RLD	E5, F4-F5
Poeck's	AC, AG, AN, FA	D4-E4, E4-F5
Vignolo's	AC, AG, AN, CA	F7

*From data of Morris et al.[4]

†AC indicates acalculia; AG, agraphia; FA, finger agnosia; RLD, right-left disorientation; AN, anomia; and CA, constructional apraxia.

‡See the Figure.

In summary, a relatively large number of distinctive symptom combinations, each of which can be regarded as a syndrome, could be elicited by stimulation at different loci in the posterior perisylvian territory. Morris et al[4] characterize this territory as "an area of importance for a variety of cortical functions" and conclude that "whether or not Gerstmann's syndrome is a 'distinct entity' is a moot question."

COMMENT

The case reports reviewed herein indicate that, on rare occasions, a more or less pure Gerstmann syndrome that can be attributed to a focal lesion in the left posterior perisylvian region is encountered. That clinicians are now able to identify relatively small lesions in this territory is due entirely to the utilization of CT and magnetic resonance imaging. Before the advent of these neurodiagnostic procedures, the presence and locus of such lesions in the living patient could only be surmised and not firmly established. As some authors[1,4] have pointed out, the rarity of cases of Gerstmann's syndrome without any accompanying deficits is probably associated with the fact that naturally occurring brain lesions are very likely to compromise a more extensive cerebral region and thus produce a larger symptom complex of which the Gerstmann deficits are only a part.

In any case, the contention that Gerstmann's syndrome can occur as a combination unaccompanied by other behavioral deficits, such as anomia, alexia, and constructional apraxia, is fully supported. The case reports also indicate that the combination can appear as a consequence of focal disease in the posterior perisylvian region of the left hemisphere. However, the syndrome also can be produced by lesions in other areas of the brain.[7,10,11,13] In a recent case report, Santos et al[14] described a nonaphasic Gerstmann syndrome produced by a left posterior thalamic lesion without involvement of the left posterior perisylvian region, as documented by magnetic resonance imaging. In an earlier case report, Sobota et al[15] described the syndrome in combination with constructional apraxia and short-term memory impairment in a nonaphasic patient in whom autopsy disclosed only a small infarct in the left postcentral gyrus. That such correlations should be found is not surprising from the standpoint of modern concepts of localization of brain function that have rejected discrete areal localization in favor of extensive neural networks. Nevertheless, Gerstmann's syndrome, either in "pure" form or with other deficits that can be attributed to posterior parietal disease, is clinically meaningful in that it points to the probability of the presence of a lesion in this area. It is a tribute to Josef Gerstmann's diagnostic acumen (or his imagination) that he drew this inference based on his own inadequate patient sample.

What of the other symptom combinations that have been, or can be, identified as syndromes indicative of posterior parietal disease? Describing an extensive parietal syndrome that included spatial disorientation, constructional apraxia, and the Gerstmann deficits, Stengel[16] maintained that Gerstmann's syndrome should not be regarded as an autonomous entity but only as a part of *his* more pervasive syndrome. Critchley[10] called attention to other symptom combinations that have been designated as syndromes but that have not been eponymically adopted as widely as has Gerstmann's syndrome, eg, Leonhard's syndrome[17] (acalculia, agraphia, and constructional apraxia) and Zeh's syndrome[18] (acalculia, agraphia, and defective facial perception). Critchley suggested that the reason for this difference was that Gerstmann's syndrome was introduced at a time "when attention was first being directed toward the complex symptomatology now associated with lesions of the parieto-temporal-occipital crossroads."[10(p197)]

Regrettably, the arduous study of Morris et al,[4] consisting of repeated observations during a period of some weeks, involved only a single patient. It would be valuable to have an idea about the degree of interindividual variability of the responses to stimulation found in a sample of patients. Notwithstanding this limitation, the findings of Morris et al are clear: Stimulation of very small areas of posterior perisylvian cortex elicited distinctive combinations of deficits, each of which deserves the designation of "syndrome" as fully as does the Gerstmann combination. It seems evident that the prominence of Gerstmann's syndrome is, as Critchley[10] suggested, a matter of historical accident. Because it occurs so rarely in pure form, Gerstmann's syndrome may in fact be less useful as a diagnostic indicator of focal parietal-temporal-occipital disease than are some other symptom combinations.

The question of whether the components of Gerstmann's syndrome should be thought of as expressions of a single basic deficit remains: a "disturbance of the body schema" according to Gerstmann and "spatial disorientation" according to Stengel.[16] While the application of these broad concepts may be appropriate in dealing with some disabilities (eg, the phantom limb, autotopagnosia, and mislocalization of tactile stimulation), neither has been found to be useful to advance the understanding of Gerstmann's syndrome.[2,19-22]

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Detection and Staging of Dementia in Alzheimer's Disease

Use of the Neuropsychological Measures Developed for the Consortium to Establish a Registry for Alzheimer's Disease

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• Our earlier studies using the Consortium to Establish a Registry of Alzheimer's Disease neuropsychological battery showed that delayed recall was a highly sensitive indicator of early Alzheimer's disease. None of the learning and memory measures in the battery were found to be useful in staging the severity of this form of dementia. This study explores the nonmemory functions (fluency, naming, and praxis) of the Consortium to Establish a Registry of Alzheimer's Disease battery and asks whether performance on any of these measures adds to the detection of early Alzheimer's disease or is sensitive to the later progression of the illness. We stratified patients with this disease according to severity (mild, moderate, severe), and compared them with age-, education-, and gender-matched control subjects (group N=49 each). Multivariate procedures and cutting scores were used to determine the efficacy of the various measures in distinguishing between the cases and control subjects. Impairment of delayed recall was again found to be the best discriminator for detecting mild cases of Alzheimer's disease. Confrontation naming was the only nonmemory factor that assisted in this discrimination. For staging the illness, a combination of measures including fluency, praxis, and recognition memory best differentiated cases with mild dementia from those with either moderate or severe stages of disease. Measures of delayed recall quickly "bottomed out" in the patients with Alzheimer's disease and proved of little value in staging the disorder. These findings are consistent with the reported pathologic progression of the illness and suggest that whereas delayed recall memory is a highly sensitive indicator of Alzheimer's disease, lexical-semantic processing and visuospatial functions are better determinants of the progressive course of this illness.

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Severe impairment in recent memory is a distinctive hallmark of Alzheimer's disease (AD) and is often regarded as the most important early manifestation of the disorder.[1-3] Recent studies attempting to differentiate patients with very mild AD from normal elderly control subjects[4,5] and to identify individuals with preclinical signs of AD[6-8] are consistent with this general view. Various paradigms with differing demands on elaborative encoding and sensory-input modality (eg, visual, tactile, and auditory), have shown that performance on measures of recent memory differentiates cases in the earliest stages of AD from normal elderly control subjects.[4-8] These data also indicate, however, that all measures of recent memory measures are not equally effective for this purpose. Our recent study of the Consortium to Establish a Registry for AD (CERAD) neuropsychological assessment battery,[9] for example, showed that impairment on tests of *delayed recall* is particularly sensitive and specific to the early stages of AD dysfunction.[4] In contrast, other memory measures such as immediate recall, intrusion errors, and recognition memory had poor overall discriminability, and none of the memory measures examined, including delayed recall, were effective in staging the severity of the disorder. The failure of these measures in staging AD is probably due to "floor effects" related to the severe memory impairment of AD that may be present even in the early stages of the disease.

In this study we explored two additional issues in the CERAD neuropsychological test battery using the same population of patients as in our previous article.[4] First, we assessed whether other cognitive measures (fluency, naming, constructional praxis) in the CERAD battery would, in combination with delayed recall, further improve the identification of the very early cases of AD. Second, since memory measures had proven to be of little use in staging severity of AD, we examined the utility of the nonmemory measures in tracking the extent of cognitive dysfunction as the disease progresses. These issues are of particular importance in assisting reliable detection of early stage AD, as well as for providing indexes of the severity of this illness.

SUBJECTS AND METHODS

Subjects

The 147 patients with AD and 49 control subjects included in our analyses were drawn from the total of 549 patients with AD and 390 control subjects entered in the CERAD national study

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Table 1.—Demographics*

	Control	Mild	Moderate	Severe
Group N	49	49	49	49
MMSE†				
Mean	28.9	25.0	21.0	13.9
SD	1.0	1.0	1.3	2.9
CDR				
Mean	0	1.0	1.3	1.7
SD	0	0.3	0.5	0.7
Sex				
Male	25	25	25	25
Female	24	24	24	24
Age, y				
Mean	71.1	71.2	71.1	71.1
SD	5.7	5.6	5.6	5.7
Education				
Mean	14.0	13.8	13.9	13.7
SD	2.9	2.5	3.0	3.0

*MMSE indicates Mini-Mental State Examination; CDR, Clinical Dementia Rating.

†The Alzheimer's disease groups are stratified according to MMSE scores. For comparison purposes with respect to the severity of dementia in the various groups, CDR scores are also included. As this table shows, the cases and control subjects were successfully matched for age, education, and gender.

between April 1987 and July 1989. All subjects were 50 years of age or older and could speak and comprehend English. The patients met diagnostic criteria for probable AD using the criteria adopted from the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association Workgroup.[10] The control subjects were either spouses of the patients with AD or community volunteers and were free of cognitive impairment at entry into the study. Diagnoses were made by the examining neurologist before inclusion in the CERAD study. Thus, the physicians assigning diagnoses used mental status measures from their own clinical evaluations, independent of the results of the CERAD neuropsychological tests.

The available pool of 549 patients was stratified into three groups according to severity of cognitive impairment as defined by Mini-Mental State Examination (MMSE) scores[11]: the "mild" group of AD cases consisted of those with MMSE scores of 24 or greater; the "moderate" group had scores between 19 and 23; and the "severe" group scored between 10 and 18. Subjects forming the smallest group, the mild group (n = 49), were then computer matched to each of the other groups with AD and control subjects on the basis of age, education, and gender. As a result of this matching procedure 147 cases of AD and 49 control subjects were included in this study (Table 1). These were the same 196 subjects used in our previous article on the CERAD memory tests.[4]

Neuropsychological Assessment

All subjects received the entire CERAD neuropsychological battery,[9] which includes the MMSE as well as *language tasks:* category fluency (animal generation) and visual naming (abbreviated Boston Naming Test[12]); a test of *constructional praxis:* drawing of four geometric forms; and a *verbal memory test*: immediate recall of a 10-item word list, delayed recall of the list, and delayed recognition/discrimination of the target items from embedded foils.

The measures analyzed in this study included the four memory measures previously shown[4] to discriminate between subject groups: delayed recall, correct recognition of target words (recognition, yes), correct discrimination of foils (recognition, no), and intrusion errors. Immediate recall did not previously discriminate well between groups and was not included in this set of analyses. In addition to the memory measures, nonmemory measures, including the total number of unique exemplars on the category fluency task (fluency), the total number correct on the visual naming procedure (naming; maximum possible, 15), and the total correct score on the constructional praxis test (praxis; maximum possible, 11) were examined.

Statistical Analysis

The results were analyzed in several ways. First, mean scores were computed for the control and demented groups on each cognitive measure. Performance on these measures was contrasted between the groups using analysis of variance. When significant differences emerged, post hoc comparisons were made using Scheffé's procedure.[13]

Second, each measure was then assigned a cutting score, based on the control subjects' performance, which corresponded to point 2.0 SDs below the mean in the control group. Correct group classification based on these cutpoints was evaluated. In this manner the relative sensitivities (percentage of patients with AD correctly classified) and specificities (the percentage of control subjects correctly identified) of the various cognitive measures could be contrasted.

Third, the most efficacious combination of measures for discriminating between normal control subjects and patients with AD and that discriminating between the different severities of AD dementia (mild vs moderate vs severe) were determined through stepwise discriminant function analyses. Although in our previous study[4] we used a *P* value of less than .15 criterion for inclusion in the discriminant analyses, we adopted a more conservative *P* value of less than .05 criterion for the present analyses. These analyses included both the memory measures successfully differentiating the groups in our initial work and the nonmemory measures. The order of variable selection in the discriminant formula was based on their partial correlation coefficients after all possible combinations had been examined. At each step of the procedure, the variable accounting for the greatest portion of unexplained variance was entered. The remaining variables were adjusted accordingly and examined for possible entry until variables meeting the entry criteria for the model had been exhausted.

RESULTS

Mean scores on the memory and nonmemory measures for each of the AD patient groups and the matched control group are summarized in Table 2. Significant overall group differences emerged for each of the cognitive measures (analysis of variance, $df = 3$; $P < .001$). Individual group comparisons revealed that the control group, with rare exception, out-performed the groups of patients with AD on the various cognitive measures, even when comparisons were restricted to the mildly affected patients.

Detecting Early AD

To establish the value of each of the cognitive measures in discriminating between control subjects and patients with mild AD, the sensitivity and specificity of each cognitive measure were assessed. Cutting scores were established for each measure (2 SDs from control mean). By analyzing the frequency distribution of scores, the percentage of patients and control subjects correctly classified at this cutpoint could be determined.

Consistent with the previous study,[4] delayed memory proved to be by far the most efficacious measure distinguishing early AD from control subjects (Table 3). This measure correctly classified 94% of the control subjects, and distinguished 86% of the patients with mild demen-

Table 2.—Mean Performance Levels (+SD) for the Elderly Control and Alzheimer's Samples

	Control	Mild	Moderate	Severe
Delay recall*	6.8 (1.9)	1.8 (1.8)†	0.7 (1.5)‡	0.5 (1.0)
Recognition*				
Yes	9.7 (0.6)	8.2 (2.4)†	7.7 (2.3)	6.9 (2.6)
No	9.7 (1.5)	7.7 (2.7)†	7.5 (2.6)	6.4 (3.0)
% Intrusions*	3.0 (4.6)	10.2 (15.5)	12.8 (18.2)	21.4 (20.2)
Language*				
Fluency	17.2 (4.0)	11.0 (3.9)†	9.6 (4.0)§	5.3 (2.7)
Naming	14.6 (0.7)	13.0 (2.2)†	12.3 (2.7)§	9.7 (3.5)
Praxis*	9.8 (1.5)	8.9 (2.0)	7.9 (2.3)§	5.3 (2.6)

*Analysis of variance $df=3$; ($P<.001$).

†$P<.05$ compared with control subjects. All measures for the moderate and severe groups were statistically different from control subjects.

‡$P<.05$ compared with mild AD group.

§$P<.05$ compared with severe AD group.

Table 3.—The Efficacy of Test Measures in Correctly Classifying Subjects Based on Cutting Scores*

	% (N)			
	Control	Mild	Moderate	Severe
Delay recall	94 (46)	86 (42)	96 (47)	96 (47)
Recognition, yes	96 (47)	39 (19)	53 (26)	73 (35)
Recognition, no	98 (48)	25 (12)	32 (16)	48 (23)
Intrusions	94 (46)	33 (16)	33 (16)	62 (29)
Fluency	100 (49)	35 (17)	49 (24)	94 (46)
Naming	92 (45)	53 (26)	55 (27)	84 (41)
Praxis	96 (47)	15 (7)	27 (13)	61 (29)

*This table illustrates the efficacy of each test measure in correctly classifying subjects based on cutoff scores 2.0 SDs below the control mean. The best overall measure in discriminating between groups is delayed recall. The other measures have poor overall discriminability.

Table 4.—Efficacy of Memory Measures in Determining Group Assignment Based on Stepwise Discriminant Function Analysis Results*

Comparables	R^2	F	P
Control subjects vs group with mild AD†			
Delay	.650	176.3	.0001
Naming	.124	13.2	.0004
Group with mild AD vs group with moderate AD‡			
Delay	.098	10.3	.0018
Praxis	.050	4.9	.0285
Group with moderate AD vs group with severe AD§			
Recognition, yes	.065	5.2	.025
Intrusions	.052	4.1	.04
Fluency	.182	20.3	.0001
Praxis	.103	10.4	.0017

*AD indicates Alzheimer's disease.

†Delay and recognition memory were shown previously to correctly classify 91% of the subjects, separating 89% of the mildly demented cases from 92% of the control subjects. In this new analysis adding in nonmemory measures, naming entered the equation but did not improve correct classification. Overall correct classification was 91%, separating 90% of the mild subjects from 92% of the control subjects.

‡The delay measure alone correctly classified 65% of the subjects, separating 47% of the mildly impaired cases from 84% of the moderately impaired cases. With praxis added into the equation, correct discrimination improved to 71%, separating 69% of the mild cases from 73% of the moderate cases.

§Overall accuracy in discriminating groups was shown previously to classify 66% of the subjects, separating 73% of the moderately impaired individuals from 59% of the severely demented patients. Accuracy when nonmemory measures were included in the analysis was much higher. Correct classification overall was 81%, separating 80% and 82% of the moderately and severely impaired individuals, respectively.

tia and 96% of both the moderately and severely demented patients from the control subjects. Although the patients had impaired recognition memory and committed more intrusion errors than did the control subjects, these measures had poor overall discriminability. Similarly, none of the nonmemory tests (fluency, naming, constructional praxis) were particularly useful in distinguishing between the patients with mild AD and the control subjects. Constructional praxis was the least efficient measure in this regard.

The cutpoint method of analysis allows examination of the various cognitive measures individually and determines their efficiency in distinguishing between patient groups and control subjects. Because group prediction may be enhanced when consideration is given to performance on multiple measures simultaneously, stepwise linear discriminant function analysis was used to determine the most effective *combination* of tests distinguishing between groups (Table 4).

As one might suspect based on the previous cutpoint analyses, delayed recall was the most discriminating variable. It accounted for the greatest percentage of the variance between groups and entered the discriminant equation first ($r^2=.6499$, $F=176.3$, $P<.0001$). This measure by itself correctly classified 91% of the subjects, separating 90% of the mild AD cases from 92% of the control subjects. The only other variable to enter the equation based on the conservative entry criteria ($P<.05$) was the confrontation naming measure ($r^2=.1235$, $F=13.2$, $P<.0004$). However, when these two measures were combined the classification matrix was no different than when delayed recall had been used alone (91% correct classification; 90% mild AD, 92% control subjects). Thus, it appears that delayed recall is the single best measure for discriminating patients with early AD from control subjects and that the other cognitive variables add little additional information in this regard.

Although delayed recall proved to be the most informative measure in distinguishing patients with early AD from control subjects, performance on the other cognitive measures, particularly on the language tests (fluency, naming) might still have some value in confirming the presence of early AD dementia. Consistent with this possibility, an examination of the 42 patients with mild AD scoring below the cutpoint on delayed recall indicated that 53% were also impaired (ie, below the 2-SD cutpoint) on fluency, 50% were impaired on naming, and 60% were impaired on either fluency or naming. Only 25% of this subgroup showed impaired constructional praxis and 67% were impaired on at least one of the three nonmemory measures.

Staging the Severity of AD Symptoms

As noted in our previous study,[4] the overall accuracy of the CERAD battery in distinguishing between mild, moderate, and severe AD groups was poor when the discriminant analyses were limited to the memory measures alone. However, the inclusion of the nonmemory CERAD measures in this study permitted better classification of the groups of cases with AD, particularly at the later stages of the disorder.

In the comparison of the mildly and moderately impaired patients, the delayed recall measure was the only memory measure to enter into the linear model. This measure alone correctly classified 65% of the subjects, separating 47% of the mildly impaired patients from 84% of the moderately impaired individuals. With the addition of nonmemory measures to the analysis, constructional praxis met the criteria for entry into the discriminant equation. The addition of this measure improved the overall discrimination slightly to 71% and resulted in correct classification of 69% of the mildly impaired patients and 73% of those with moderate impairment.

In the later stages of the disease (ie, the comparison of moderately and severely impaired patients), the combination of correct identification of the target words (Rec-Yes) and intrusion errors was shown previously[4] to discriminate between the groups, albeit not very powerfully. Adding fluency and constructional praxis measures into the discriminant model substantially improved the discrimination between these groups (Table 4). Correct classification increased from 66% when restricted to memory measures alone to 81% with the addition of the fluency and constructional praxis measures. This combination of measures correctly classified 80% of the moderately impaired patients and 82% of the severely impaired patients. Naming of objects, although adding to the early detection of cases, was not as good as measures of fluency and constructional praxis for staging progression of the disease and did not enter into the discriminant equation.

COMMENT

All neuropsychological measures included in the CERAD battery distinguish patients who were diagnosed as having probable AD from normal elderly control subjects. However, of all the cognitive variables included in the battery, only the measure of delayed recall (as reported previously) is by far the best discriminator in detecting the *mild cases* of AD. Our results suggest that in patients with subtle cognitive impairment associated with AD, predictive accuracy can be enhanced by focusing on measures of delayed recall. Other measures of memory, including immediate recall, recognition memory and intrusions, and nonmemory measures such as fluency or constructional praxis, are not as powerful in terms of differentiating the patients with very mild AD from control subjects. Confrontation naming is the only other CERAD measure that has some limited utility in the identification of early cases. Even so, this language index, by itself, had little predictive power, and when combined with the more robust delayed recall measure it did not appreciably improve the overall discrimination of the patients with early stage AD from the normal elderly control subjects.

Whereas the nonmemory measures lack sensitivity and specificity in detecting early cases of AD, these measures are of value in confirming the presence of the disease in patients with very poor scores on delayed recall. Based on our findings, it appears that at least 60% of the patients with mild AD with impaired delayed recall also have significantly impaired performance on either the fluency or naming measures. This finding suggests that for cases in which the clinical presentation is ambiguous, performance on these other cognitive measures may provide useful adjunctive information regarding the patient's cognitive status. In the early stages of AD where memory impairment may be a rather isolated finding, the use of the additional CERAD measures may act to enhance diagnostic confidence.

In addition, the nonmemory tests in the CERAD battery appear to be useful in the staging of the illness. Fluency and constructional praxis, in particular, improve the discrimination between moderately and severely impaired AD patients. These findings are consistent with other articles that have explored the evolution of cognitive deficits in AD and have demonstrated that impairment in neocortically mediated functions, such as language and praxis, emerges later in the disease course than do memory deficits.[14-17] The changes reported in this study also parallel the recent findings obtained through longitudinal observations,[18] suggesting precipitous declines occur in language functions (object naming) early in AD and declines on visuospatial tests occur later in the illness. Finally, the results correspond to the recent pathologic data[19-21] and neuroimaging studies using emission tomography,[15,16] which indicate a consistent pattern of cortical vulnerability. Affected in descending order are the mesial temporal lobe structures (entorhinal cortex, hippocampus, amygdala) mediating memory function, followed by the higher order association cortices (likely related to the language and visuospatial impairments of AD), and finally the primary sensory cortices. Which particular items on the CERAD naming and constructional praxis tests are failed at the various stages of disease and their neuroanatomic correlates require further exploration. However, previous neuropsychological analyses indicate that the more difficult items, such as performance on the low-frequency exemplars of the naming task, are the most vulnerable to disease progression.[9]

In generalizing the data presented herein to other populations, it should be noted that MMSE scores were used to stratify subjects in terms of disease severity. Other investigators may prefer to use functional criteria, such as the Clinical Dementia Rating scale,[22] rather than MMSE scores for this purpose. Regardless of stratification method, we expect the results to be similar. Evidence of this was found in a previous study[23] where we examined the memory measures in patients with AD and control subjects grouped by Clinical Dementia Rating scale scores and the results with these indexes were as robust as with MMSE stratification.

The results of this study suggest that the CERAD neuropsychological battery is a brief and useful tool for the identification of early cases of AD and also for staging disease severity with measures specialized for each purpose. Of the measures included in the battery, delayed recall proved to be by far the most sensitive measure in detecting early AD, but because all AD cases performed very poorly on this measure it appeared to have little practical value in the later staging of the illness. However, the other cognitive measures from the battery, particularly naming (in the early to moderate stages of AD) and constructional praxis and fluency (at the later stages of the illness) were useful in confirming the presence of AD dementia and staging the disease. Which particular items on these procedures are most sensitive to the disease progression remain to be determined in future studies. Regardless of the outcome of such investigation, our findings indicate that the CERAD battery is capable of characterizing patients with AD over the course of the illness. Because of the brevity of the instrument, we suggest that it may be an economical method to consider in longitudinal research designs or in epidemiologic studies in which large groups of patients with AD are under evaluation.

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Diagnosis of Dementia in a Heterogeneous Population

Development of a Neuropsychological Paradigm-Based Diagnosis of Dementia and Quantified Correction for the Effects of Education

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• A brief diagnostic battery of neuropsychological tests was developed for a large-scale epidemiological study of dementia. We operationally defined dementia as defective memory and defective performance in at least two other areas, including orientation, abstract reasoning, construction, and language. Criterion scores for defining defective performance on each test were developed. In a pilot study that used 51 different subjects with a working diagnosis based on physicians' assessment (ie, 32 demented and 29 nondemented subjects), the test-based diagnosis agreed with the working diagnosis in all but two cases. The test battery was then applied to 430 healthy elderly subjects. Eighteen percent of those with 8 or less years of education met criteria for dementia compared with 5% of those with more than 8 years of education. We computed education-corrected scores for each test with the use of residuals from the regression of each test score on education. Based on corrected scores, 12 subjects were reclassified as nondemented and 11 as demented. Subjects who were reclassified as demented were significantly more impaired in activities of daily living than nondemented subjects who were not reclassified. Activities of daily living in subjects who were reclassified as nondemented did not differ from those in demented subjects who were not reclassified. These findings suggest that the neuropsychological battery may have utility in the diagnosis of dementia. However, neuropsychological performance may be influenced by education, and some form of adjustment, such as correction for activities of daily living, may be required in epidemiological studies.

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Large-scale epidemiological studies of dementia have relied on screening tests for diagnosis, but a more definitive diagnosis may require extensive neuropsychological evaluation. In planning a community-based study of dementia, we developed a relatively short (generally, <1 hour) but comprehensive neuropsychological evaluation for diagnosis. This evaluation was also translated into Spanish.

See also p 461.

We employed operational criteria for diagnosis that made use of objective test scores to ensure that (1) study criteria for dementia were objective and replicable, and (2) criteria would not "drift" over time as a function of the experience and interaction of the examiners.

This article has two parts. First, we describe the neuropsychological battery and operational criteria, and we report results of a pilot study that was designed to determine if the criteria could produce diagnoses similar to those derived by our more standard and lengthy clinical evaluation. Second, we summarize our experience with this battery in a large group of elderly subjects and explore the possible influence of education on test results.

NEUROPSYCHOLOGICAL BATTERY

The neuropsychological battery was selected from subsets of items from standardized neuropsychological tests to assess intellectual functions that are typically affected in dementia. Average administration time was 1 hour.

For each test, all items and instructions were translated into Spanish and then translated back to ensure accuracy.

Memory

Verbal Memory.—The Selective Reminding Test was used.[1] Subjects were given six trials to learn a list of 12 unrelated words. After each attempt at recalling the list, the subject was reminded only of the words that were not recalled and then asked to attempt again to recall the entire list. To assess short-term verbal memory, two performance measures were used: (1) total recall and (2) retrieval from long-term storage. To assess long-term verbal recall, delayed recall was assessed 15 minutes after completing the Selective Reminding Test; recognition of words that were not recalled was then tested with the use of multiple-choice arrays.

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Nonverbal Memory.—A multiple-choice version of the Benton Visual Retention Test[2] was used to assess nonverbal memory in a format that did not rely on constructional abilities. The subject viewed a design for 10 seconds. It was then removed, and the subject was asked to recognize the design in an array that included three distractors. Ten items were used, corresponding to Form D of the original Benton Visual Retention Test.

Orientation

Ten items from the Mini-Mental State Examination[3] were used to assess orientation to time and place.

Visuospatial Ability

Construction.—In this test, the subject copied five designs that were selected from the Rosen Drawing Test[4] to span a range of difficulty from simple shapes and topological concepts to overlapping, euclidean, and three-dimensional designs.

Benton Visual Retention Test Matching.—For each of 10 items, the subject matched a larger picture to one in an array of four smaller pictures. Items corresponded to Form C of the original Benton Visual Retention Test.[2]

Language

Naming.—Fifteen selected items from the Boston Naming Test[5] were used.

Verbal Fluency.—*Controlled Oral Word Association.*—For this association,[6] the subject was given 1 minute each to name as many words as possible, beginning with the letters C, F, and L. For Spanish-speaking subjects, the letters P, S, and V were used. Percentile scores were derived based on age- and education-adjusted norms.

Category Naming.—The subject was allowed 1 minute each for three categories: animals, food and clothing. Scores were expressed in terms of the mean number of words reported in the three categories.

Comprehension.—The first six items of the Complex Ideational Material subtest of the Boston Diagnostic Aphasia Evaluation[7] were used to assess verbal comprehension. These items required only yes/no answers to relatively simple questions.

Repetition.—The high-frequency items from the Boston Diagnostic Aphasia Evaluation Repetition of Phrases subtest[7] were used.

Abstract Reasoning

Wechsler Adult Intelligence Scales–Revised.—This Wechsler Adult Intelligence Scale–Revised[8] subtest required the subject to identify relevant similarities between pairs of items. Age-scaled scores were used.

Identities and Oddities.—In this subtest of the Mattis Dementia Rating Scale,[9] the subject was asked to identify the two of three items that were the same. After eight trials were completed, the same items were administered again, with the subject identifying the one item that was different.

DIAGNOSIS

We used a series of criterion scores to determine whether a subject's intellectual function was impaired to the extent that was required to meet criteria for dementia. Criterion scores were determined based on a review of the performance of 172 patients and controls who had been evaluated in previous clinical studies or in our Memory Disorders Clinic (New York State Psychiatric Institute, New York City). In this group, 32 were nondemented elderly controls, 77 had probable Alzheimer's disease,[10] 39 had Parkinson's disease (PD), 14 had PD and dementia, and 10 had PD and major depression. For each test, mean scores and variability in each group were inspected, and the score that best separated nondemented and demented groups was selected as the criterion score.

Based on criteria for dementia according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition,*[11] memory was considered to be the key-defining feature of dementia; we required that two of three of the defined memory "areas" ([1] short- and [2] long-term verbal memory and [3] short-term nonverbal memory) be defective to meet criteria for dementia. In addition, performance on at least two of the following areas also had to be impaired: orientation, construction, abstract reasoning, and language. The diagnostic paradigm, including criterion scores, is summarized in Table 1. The maximum possible score for each test is also included in Table 1, where applicable.

The requirement that two aspects of memory be impaired, as well as at least two other cognitive functions, was intended to ensure that subjects were not misclassified on the basis of poor performance on a single measure. In addition, it was designed to simulate to some degree the approach that a clinician would take toward investigating a pattern of neuropsychological performance in a clinical dementia evaluation.

STUDY 1: PILOT STUDY OF NEUROPSYCHOLOGICAL BATTERY

Methods

Subjects.—Fifty-one individuals were included in this study. All subjects were well known to us and had established diagnoses based on findings from full clinical evaluation and extensive neuropsychological testing. Five subjects were healthy elderly individuals, 12 had probable Alzheimer's disease,[10] 17 had stroke (11 were demented and six were nondemented), and 17 had PD (eight were demented and nine were nondemented). Demographical information is summarized in Table 2.

Procedures.—The neuropsychological battery, as described above, was administered to each subject by a technician who was unaware of the subject's dementia status. The diagnostic paradigm, as outlined in Table 1, was applied to each subject's test results to determine if that subject's performance met criteria for dementia.

Results

The mean age did not differ significantly across groups, but the group with stroke dementia had significantly less years of education (Table 2). The mean performance of the groups on the neuropsychological battery is summarized in Table 2. The t test comparisons of demented and nondemented subjects were significant for every neuropsychological test ($P<.05$ for all). One-way analyses of variance that compared performance of all groups on each test were significant in each case ($P<.05$ for all). Duncan's multiple-range test post hoc comparisons are summarized in Table 2.

On a case-by-case basis, all but two demented subjects met criteria for impairment in memory and two other cognitive categories. The relationship between the diagnosis derived from the neuropsychological battery and the previously established diagnosis was highly significant ($\chi^2=43$, $P<.01$).

There were no false positives, that is, cases where the paradigm identified nondemented subjects as demented. However, two cases of probable Alzheimer's disease were not correctly classified. Both cases had been diagnosed clinically on the basis of a history of progressive intellectual and functional decline; however, these subjects did not perform at a defective level on most tests in the more extensive neuropsychological battery that was used in our Memory Disorders Clinic, and these cases would probably not have been diagnosed as demented based on results of neuropsychological testing alone.

Table 1.—Operational Definitions of the Impairment in Memory and the Two Other Cognitive Categories Required for the Diagnosis of Dementia*

Function	Measure†	Score	
		Cutoff	Maximum
Memory impairment	Two of the following		
	Immediate verbal		
	Both of the following		
	SRT total recall[1]	<25	72
	SRT long-term retrieval[1]	<15	72
	Remote verbal		
	Both of the following (if delayed recall = 0, then remote verbal is impaired)		
	SRT delayed recall[1]	<4	12
	Delayed recognition	<8	12
	BVRT multiple-choice recognition[2]	<7	10
Impairment in two of the following			
Orientation	Orientation test[3]	<8	10
Construction	One of the following		
	Rosen Drawing Test[4]	<3	5
	BVRT multiple-choice matching[2]	<7	10
Abstract reasoning	One of the following		
	WAIS-R Similarities (age scaled)[8]	<7	19
	Mattis Identities and Oddities[9]	<12	16
Language	One of the following		
	BDAE repetition of high-probability phrases[7]	<7	8
	BDAE complex ideational material[7]	<5	6
	Boston Naming Test[5]	<11	15
	Verbal fluency (one of the following)		
	CFL (percentile score)[6]	≤16th percentile	. . .
	Category naming (mean of three trials)	<12	. . .

*SRT indicates Selective Reminding Test (12 items, six trials); BVRT, Benton Visual Retention Test (10 items); WAIS-R, Wechsler Adult Intelligence Scale–Revised; BDAE, Boston Diagnostic Aphasia Evaluation; and CFL, Controlled Oral Word Association.

†Superscript numbers refer to test references.

These findings suggested that performance on this battery of tests might effectively determine whether a subject had suffered cognitive decline consistent with a diagnosis of dementia.

We did not attempt to account for the effects that strokes might have had on test performance. Similarly, we did not address the application of this approach to Spanish-speaking subjects or those with low levels of education.

STUDY 2: ADMINISTRATION TO COMMUNITY-DWELLING ELDERS

In this study, the neuropsychological paradigm, as described and piloted above, was administered to a large group of elderly subjects who lived in the northern Manhattan (NY) community of Washington Heights Inwood.

Methods

Subjects.—Subjects were selected from volunteers who participated in the Washington Heights Inwood Project, a community-based prospective investigation of Alzheimer's disease and dementias associated with PD and stroke; this project consisted of three subprojects, with coordinated but independent recruitment procedures. In the North Manhattan Aging Project, potential subjects were referred by community-based service providers, and recruitment was limited to a geographically defined area of northern Manhattan. In the North Manhattan Aging Project, subjects who were free of dementia in the study sample were used as controls. The PD project actively solicited potential subjects with PD through hospital surveillance, community-based service providers, and news media. Recruitment was also restricted to northern Manhattan. The Stroke and Aging Research Project consisted of a hospital-based sample of stroke patients. In the Stroke and Aging Research Project, a "control" subject was recruited for each stroke subject; the control was often a spouse, friend, or neighbor, but controls were also solicited by advertising and mailings. For the PD study, controls who lived in northern Manhattan were solicited in a similar manner.

The present study sample was selected from all individuals who participated in the three subprojects and who met the following criteria: subjects with PD or with a history or clinical signs of stroke were excluded so that the potential influence of these diseases on neuropsychological test performance could be eliminated.

We excluded subjects for whom complete data on all neuropsychological tests were not available, since the paradigm and subsequent education correction approaches could not be fully applied to incomplete data. Among those for whom testing was attempted, 6.4% refused to complete one or more of the tests that constituted the battery, and 14.6% were unable to complete one or more of the tests. Severe cognitive impairment appeared to be the reason for failure to complete the test battery; 73% of those subjects who were unable or unwilling to complete the tests were subsequently diagnosed as demented based on the physician's assessment and other clinical data—more than seven times the rate of dementia among those subjects who were able to complete the battery.

Subjects were also required to have completed a semistructured assessment by a physician. All subjects had to be older than 55 years of age, and they had to speak English or Spanish. A total of 430 individuals met all criteria for inclusion in the study sample. Demographic characteristics of the study sample are summarized in Table 3.

Procedures.—The neuropsychological battery, as described above, was administered to each subject. Before administration, an attempt was made to determine if the subject felt she or he would perform better in English or Spanish, and this determined

Table 2.—Performance of Study 1 Patients on Neuropsychological Battery*

	Group†					
	Control	pAD	PD	PD + Dementia	Stroke	Stroke + Dementia
Group demographics						
n	5	12	9	8	11	6
Age, y	63.0 (7.6)	69.4 (6.9)	65.4 (7.4)	69.4 (7.9)	66.6 (11.4)	73.8 (8.5)
Education, y	14.6 (2.4)^{a}	15.1 (4.6)^{a}	13.8 (2.1)^{a}	17.1 (3.6)^{a}	12.6 (4.5)^{ab}	8.5 (4.7)^{b}
Abstract reasoning						
WAIS-R Similarities	11.6 (2.6)^{a}	8.6 (2.4)^{ab}	10.4 (2.2)^{a}	6.4 (4.1)^{b}	9.4 (3.8)^{ab}	6.5 (1.9)^{b}
Mattis Identities	15.6 (0.9)^{a}	13.0 (2.4)^{a}	15.4 (0.9)^{a}	8.5 (7.2)^{b}	14.8 (1.5)^{a}	12.6 (3.4)^{a}
Orientation	9.8 (0.4)^{a}	4.0 (2.2)^{c}	9.8 (0.5)^{a}	4.6 (2.8)^{c}	9.2 (0.9)^{a}	7.0 (1.8)^{b}
Memory						
SRT						
Short-term recall						
Total recall	53.4 (11.2)^{a}	25.2 (9.8)^{c}	43.1 (6.3)^{b}	18.8 (7.6)^{c}	37.2 (13.2)^{b}	24.0 (5.4)^{c}
LT retrieval	47.2 (14.9)^{a}	7.1 (5.2)^{c}	29.2 (11.2)^{b}	4.9 (4.0)^{c}	26.1 (13.9)^{b}	5.8 (4.2)^{c}
Delayed recall						
Recall	9.6 (1.3)^{a}	0.5 (1.2)^{c}	7.0 (3.4)^{b}	0.4 (0.4)^{c}	5.6 (3.5)^{b}	2.0 (1.8)^{c}
Recognition	11.8 (0.4)^{a}	7.1 (2.8)^{b}	11.4 (1.0)^{a}	4.3 (3.7)^{c}	11.1 (1.6)^{a}	9.8 (1.3)^{a}
BVRT, recall	7.7 (1.7)^{ab}	5.9 (2.2)^{bc}	8.0 (1.1)^{ab}	2.9 (3.1)^{d}	8.2 (1.6)^{a}	5.3 (1.4)^{c}
Visuospatial						
Rosen Drawing Test	3.6 (0.9)^{a}	2.1 (1.2)^{b}	2.6 (1.0)^{ab}	0.9 (1.0)^{c}	2.6 (1.1)^{ab}	1.0 (0.6)^{c}
BVRT, matching	9.0 (0.7)^{a}	6.4 (2.4)^{bc}	8.8 (1.3)^{a}	4.4 (3.1)^{c}	8.1 (2.3)^{ab}	5.7 (1.4)^{c}
Language						
fluency						
CFL (raw mean score)	10.5 (2.8)^{ab}	9.5 (4.6)^{a}	12.0 (2.9)^{a}	3.6 (1.8)^{c}	10.3 (4.9)^{ab}	7.2 (2.4)^{bc}
Categories	17.0 (2.9)^{a}	10.4 (5.4)^{b}	15.4 (5.4)^{a}	5.4 (2.7)^{c}	15.6 (5.0)^{a}	6.3 (1.5)^{bc}
Repetition	8.0 (0.0)^{a}	7.0 (1.1)^{a}	7.6 (0.7)^{ab}	6.5 (1.5)^{b}	7.6 (0.8)^{ab}	6.5 (0.8)^{b}
Comprehension	6.0 (0.0)^{a}	4.5 (2.0)^{ab}	5.7 (0.7)^{a}	3.3 (2.1)^{b}	5.6 (0.7)^{a}	4.8 (1.2)^{a}
Naming	14.4 (0.9)^{a}	11.8 (4.2)^{ab}	14.2 (1.4)^{a}	11.0 (2.9)^{ab}	13.6 (2.3)^{a}	8.8 (4.4)^{b}

*For each one-way analysis of variance comparing groups on a single variable that is significant at $P < .05$, superscript characters summarize post hoc comparisons; means with the same letter do not differ significantly. Except for n, data are given as mean (SD). pAD indicates probable Alzheimer's disease; PD, Parkinson's disease; WAIS-R, Wechsler Adult Intelligence Scale–Revised; SRT, Selective Reminding Test; LT, long-term; BVRT, Benton Visual Retention Test; and CFL, Controlled Oral Word Association.

†The superscript alphabet letters summarize post hoc comparisons. The means with similar letters do not differ significantly from each other.

the language in which the test was administered. The paradigm, as described above, was used to determine if each subject met criteria for dementia.

Separate from the neuropsychological testing, a physician completed three measures of functional capacity or activities of daily living: the Blessed Dementia Rating Scale (Part I, Sections A and B),[12] the Schwab and England Activities of Daily Living Scale,[13] and the Barthel Index.[14] For the Barthel Index items, scores were reported simply as the number of assessed activities in which disability was reported. The short version of the Blessed Memory Information and Concentration Test[15] was also administered. The physician used this information, along with that obtained during a medical and neurological examination and elicitation of medical/neurological history, to determine separately whether each subject met criteria for dementia.

Data Analysis.—The major focus of the analyses was on the influence of educational attainment on meeting neuropsychological criteria for dementia. Comparisons of dementia rates by educational ranges, as well as by age and ethnicity, were initially done with χ^2 tests for independence.

To determine the potential impact of education on the neuropsychological test-based diagnoses, the following approach was developed to derive an education-adjusted diagnosis. First, the linear regression equation for the prediction of each test score by education was calculated. For these calculations, subjects whom the neurologist considered to be demented were excluded ($n=42$), since the relationship between education and performance would be attenuated among demented individuals. We considered adjusting education for the presumed variation in educational attainment in different age groups, but in the present group there was only a minimal relationship between age and education ($r=.21$, $P<.01$); adjusting education for age had no influence on the education-adjusted diagnostic outcome, and we wished to limit the complexity of the adjustment process.

Based on the linear regression equations, each subject's residual score for each test was calculated. This residual score was the difference between the actual score and the score predicted by education in the regression equation. The use of residual scores had two advantages. First, they were, in effect, "education free" in that the correlation between the residual scores and education was 0. Second, the residual scores corrected for education at both ends of the range: subjects with higher levels of education must have performed at a higher level on a test to receive a residual score that was equivalent to that based on a lower raw score in an individual with fewer years of education.

The residual scores for each test were then transformed so that the new distribution had the same mean and SD as the distribution of the original raw test scores. A set of education-adjusted test scores was calculated for each of the 430 subjects, and then the criterion scores that were used in the neuropsychological paradigm were applied. The relationship between a test score, before and after education adjustment, and education is demonstrated in the Figure.

Results

Overall, 45 subjects fulfilled the neuropsychological paradigm criteria for dementia.

As might be expected, there was an increased frequency of in-

Table 3.—Demographic Characteristics of Subjects for Study 2*

Characteristic	Mean/ Frequency	SD/%
Age, y	73.6	7.9
Education, y	10.2	4.7
Score		
Short Blessed (BMIC)	4.9	5.0
BDRS	1.3	1.9
Schwab and England's ADL scale[13]	86.3	18.5
Barthel Sum Index[14]	0.6	1.6
Sex		
M	117	27.2
F	313	72.8
Predominant language spoken		
English	276	64.2
Spanish	130	30.2
Other	22	5.1
Unknown	2	0.5
Race ethnicity		
Non-Hispanic W	158	36.7
Non-Hispanic B	123	28.6
Hispanic	141	32.8
Other/unknown	8	1.9

*Data for age, education, and scores are given as means and SDs; data for sex, language, and race ethnicity, as frequencies and percentages. BMIC indicates Blessed Memory Information and Concentration Test; BDRS, Blessed Dementia Rating Scale; and ADL, Activities of Daily Living.

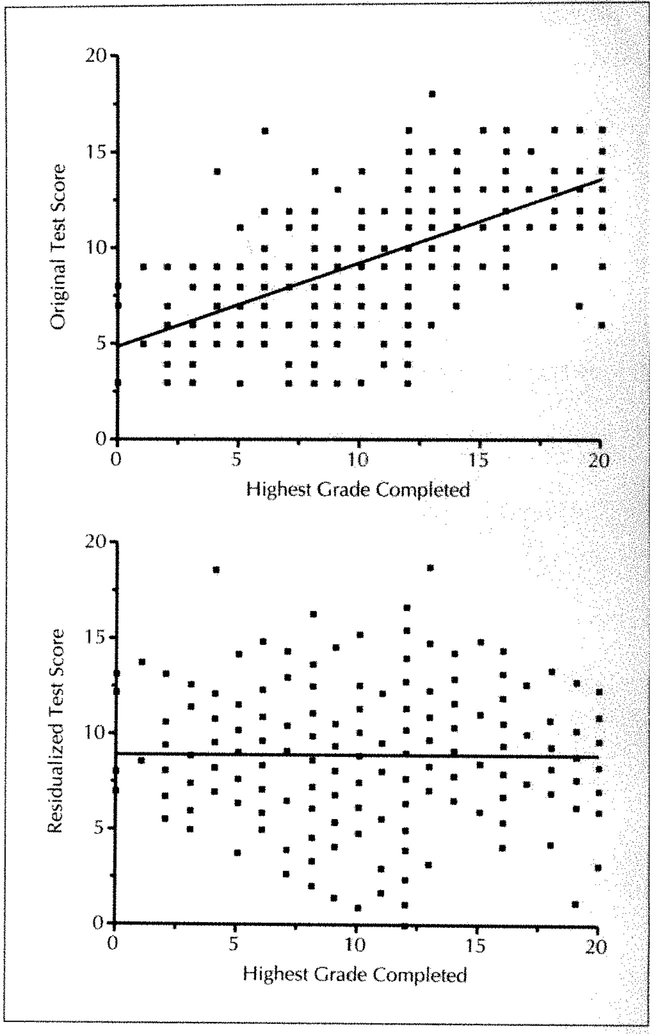
tellectual impairment in older subjects when age was subdivided into five ranges ($\chi^2 = 36.2$, $P < .01$) (Table 4). The relation between ethnic self-identification and the diagnosis of dementia (Table 5) approached significance ($\chi^2 = 7.4$, $P < .06$). However, as an analysis described below will indicate, this was a function of the differing educational level for these groups.

There was a strong relationship between years of education, subdivided into four ranges, and dementia, with higher frequencies in those subjects with lower levels of education ($\chi^2 = 21.0$, $P < .01$) (Table 6).

To evaluate the extent to which this finding was a function of the influence of educational attainment on test performance, we derived an "education-corrected" diagnosis by applying the criterion scores to test scores that were corrected for education by the statistical methods described above. Performance on every test in the neuropsychological battery correlated significantly with education. Correlation coefficients ranged from a low of .22 for repetition to a high of .67 for the Similarities subscale of the Wechsler Adult Intelligence Scale–Revised. As summarized in Table 7, the education correction resulted in a change in diagnosis in 23 cases (5.3%): 11 from not demented to demented and 12 from demented to not demented. Subjects who were reclassified as demented had more years of education: two had some high school, four were high school graduates, and five had at least some college. Conversely, subjects who were reclassified as nondemented all had 8 or less years of education.

In the subjects who were reclassified as demented, six were white, one was black, three were Hispanic, and one classified himself as neither white, black, or Hispanic. In those subjects who were reclassified as nondemented, one was white, six were black, and five were Hispanic. All subjects were at least 70 years old.

To explore how reclassified subjects differed from comparable subjects who were not reclassified, two sets of comparisons were made. Originally nondemented subjects who were reclassified as demented were compared with nondemented subjects who were not reclassified. Similarly, demented subjects who were reclassified as nondemented were compared with demented subjects who remained in that category.



Relationship between the Wechsler Adult Intelligence Scale–Revised Similarities subscale score (age scaled) and educational level of subject before (top) and after (bottom) adjustment for educational level. The line through each figure part represents the least squares regression line for predicting test scores from education. Each point on the graph represents one or more of the 430 subjects. Top, R=*.43. Bottom,* R=*.00.*

Table 8 summarizes comparisons of the 11 subjects who were reclassified from nondemented to demented with 237 selected subjects who remained classified as nondemented. The comparison group was restricted to those in the same education range and to subjects aged 60 years and older. Distributions of ethnicity and language spoken were comparable in the two groups. The two groups differed significantly on the Schwab and England Activities of Daily Living Scale. There was also a large, significant disparity between the two groups on the short version of the Blessed Memory Information and Concentration Test.

In a similar set of comparisons, the 12 subjects who were reclassified from demented to nondemented were contrasted with 19 who remained classified as demented (Table 8). Since no reclassified subjects had more than 8 years of education, subjects with more than 8 years of education were excluded from the comparison group. In addition, the comparison group was restricted to subjects who were at least 70 years old. Neither ethnicity nor language spoken differentiated the two groups, nor did the measures of functional capacity and mental status.

The relation between self-designated ethnicity and the

Table 4.—Distribution of Dementia Diagnosis by Age Ranges*

	Age Range, y					
	≤59	60-69	70-79	80-89	90+	Row Total
Not demented	7 1.8 87.5	140 36.4 98.6	163 42.3 90.6	67 17.4 76.1	8 2.1 66.7	**385** 89.5 . . .
Demented	1 2.2 12.5	2 4.4 1.4	17 37.8 9.4	21 46.7 23.9	4 8.9 33.3	**45** 10.5 . . .
Column Total	**8** 1.9	**142** 33.0	**180** 41.9	**88** 20.5	**12** 2.8	**430** 100.0

*Data are given as values for frequencies and row and column percentages. In each cell, row, and then column, percentages are listed beneath the frequency.

Table 5.—Distribution of Dementia Diagnosis by Self-designated Ethnicity*

	Race Ethnicity				
	Non-Hispanic W	Non-Hispanic B	His-panic	Other/ Unknown	Row Total
Not demented	148 38.3 93.7	103 26.8 83.7	127 33.0 90.1	7 1.8 87.5	**385** 89.5 . . .
Demented	10 22.2 6.3	20 44.4 16.3	14 31.1 9.9	1 2.2 12.5	**45** 10.5 . . .
Column Total	**158** 36.7	**123** 28.6	**141** 32.7	**8** 1.9	**430** 100.0

*Data are given as values for frequencies and row and column percentages. In each cell, row, and then column, percentages are listed beneath the frequency.

Table 6.—Distribution of Dementia Diagnosis by Education Range*

	Level of Education				
	≤8 y	Some High School	High School Graduate	Some College	Row Total
Not demented	139 36.1 81.8	58 15.1 93.5	80 20.8 90.9	108 28.1 98.2	**385** 89.5 . . .
Demented	31 68.9 18.2	4 8.9 6.5	8 17.8 9.1	2 4.4 1.8	**45** 10.4 . . .
Column Total	**170** 39.4	**62** 14.4	**88** 20.4	**110** 25.6	**430** 100.0

*Data are given as values for frequencies and row and column percentages. In each cell, row, and then column, percentages are listed below each frequency.

Table 7.—Comparison of Original and 'Education-Corrected' Diagnoses

	Corrected Diagnosis		
Original Diagnosis	Not Demented	Demented	Row Total
Not demented	374	11	**385**
Demented	12	33	**45**

education-corrected diagnosis of dementia was explored with a χ^2 analysis, and it was no longer significant ($\chi^2=3.5$, $P<.33$).

COMMENT

Our results suggest that this neuropsychological paradigm can be used in a large population with a wide range of age, ethnicity, and education. The validity of the paradigm-based diagnoses will require further study, however. In the first part of this study, we compared diagnoses based on the paradigm with those derived by more standard clinical methods, and we found good consistency between the two diagnostic methods. To the extent that the working clinical diagnoses were accurate, this suggests that the neuropsychological paradigm produces valid diagnoses. An accompanying report[16] evaluates the reliability of the neuropsychological paradigm in reference to a clinical diagnosis derived by a physician's standard dementia evaluation, including a mental status screen.

The major focus of the second study was to evaluate factors that could potentially influence test performance and consequently bias a paradigm-based diagnosis. Dementia was more common with advancing age, an expected observation. However, the higher prevalence of dementia in the subjects with fewer years of education is more problematical. Several studies have obtained similar findings.[17,18] It is possible that in individuals with more education, the dementing process must be further advanced before it is clinically detectable, since there is a higher baseline from which intellectual function must decline.[19] Education could also be in the causal pathway for dementia, but this has not been determined. While these concepts are intriguing, it must first be demonstrated that the diagnostic process is not biased against subjects with lower educational levels. For example, if subjects simply cannot comprehend the tasks that they are confronted with because of lack of prior exposure to test materials, then the diagnostic process is at fault.

While the present study cannot definitively address these issues, it does attempt to quantify the relation between educational attainment and the paradigm-based diagnosis. Findings indicate that only a small percentage of individuals, ie, 5%, were potentially misclassified due to education's effects on test performance. However, the relatively large number of low-education subjects who were reclassified as nondemented suggests that the unadjusted neuropsychological paradigm might be overdiagnosing dementia in the lower range of education. In addition, underdiagnosis of dementia may occur in the higher education ranges.

It is simplistic to assume that a statistical manipulation could adequately adjust for the effects of education. Education may serve as a proxy for many other sociocultural variables, including general intelligence, social opportunity, and societal expectations. Our ability to measure educational attainment is poor. The present analyses assumed the equivalence of education no matter where it was obtained. Also, the calculations treated years of education as an interval-level variable in which each year of

Table 8.—Comparison of ADL and Mental Status Scores in Subjects Who Were Reclassified and Education-Matched Subjects Who Were Not Reclassified*

	High Education: Reclassified From Nondemented to Demented?		Low Education: Reclassified From Demented to Nondemented?	
	Yes	No (Still Nondemented)	Yes	No (Still Demented)
Schwab and England's ADL scale[13]	78.2 (22.3)	91.5 (15.1)†	73.3 (21.2)	68.9 (23.5)
BMIC	9.0 (6.6)	2.8 (3.1)†	11.6 (5.4)	14.4 (6.9)
BDRS	2.0 (2.1)	0.6 (1.1)	2.5 (2.2)	3.5 (2.8)
Barthel Sum Index[14]	2.0 (3.6)	0.2 (1.0)	0.4 (1.2)	1.2 (1.7)

*ADL indicates Activities of Daily Living; BMIC, Blessed Memory Information and Concentration Test; and Blessed Dementia Rating Scale. Score values are given as means (SDs).

†$P<.05$ (for *t* tests).

education contributed an equal amount to total educational attainment. Given these drawbacks, the present analysis might best be viewed as an estimation of the degree to which educational attainment might possibly influence a neuropsychological paradigm-based diagnosis. We therefore do not consider the education correction paradigm, as described here, as definitive, and we await follow-up data on our subject cohort to confirm diagnoses and subsequently to refine the diagnostic paradigm.

One measure in the neuropsychological battery is a percentile score that is education adjusted (controlled oral word association). When the battery was constructed, we found that this score discriminated between demented and nondemented subjects better than the raw score. At that time, we did not anticipate the application of the education correction approach, as reported here. Still, we think that it is appropriate to include this percentile score in the education correction process because it still correlated strongly and significantly with education ($r=.41$, $P<.01$).

We excluded subjects who did not complete the entire neuropsychological battery from this study because it would have complicated the attempt at education correction. In the context of our epidemiological studies, the presumed reason for the subject not completing a test was recorded. If it was clear that the subject was incapable of completing a particular test because of a visual, auditory, or motor impairment, then that test was excluded from diagnostic consideration. Memory and other cognitive impairment in intact sensory modalities were required for the diagnosis of dementia. However, if a subject could not grasp or comply with task demands when there was no mitigating sensory, motor, or language disability, we considered that subject to have scored below the criterion for that test.

Subjects who were reclassified as demented were rated as less able to perform independently and to take care of daily activities than their peers who remained classified as nondemented. This observation adds support to the reclassification and points to the utility of a multidisciplinary approach to diagnosis, with convergent evidence from several domains required for the diagnosis of dementia. Relatively acceptable performance on the tests might be misleading in a poorly functioning individual who is well educated.

This observation was not repeated in the subjects who were reclassified as nondemented. The functional and activities of daily living measures did not differ significantly between the reclassified group and those who remained classified as demented. In theory, measures of function should be less biased by education than measures of cognition, because they typically assess the performance of activities that have little apparent relation to educational status. There is some evidence, however, that these measures are also subject to bias.[20] In any case, the present analyses suggest that ancillary functional testing would not have influenced or modified the neuropsychological paradigm-based diagnosis before application of education correction. One important consideration is that functional capacity might be given different weighting in the diagnostic process in individuals of different educational or cultural background. This issue is addressed in part in an accompanying article.[16]

The correction for education, as reported here, resulted in diagnostic reclassification in only a small percentage of the subjects. This bodes well for the utility of the present neuropsychological battery as part of a multidisciplinary diagnostic approach that uses neuropsychological performance, along with functional, medical, and psychiatric information. However, the preponderance of reclassification of presumably demented individuals suggests that the diagnostic paradigm requires further attention and development.

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Diagnosis of Dementia in a Heterogeneous Population

A Comparison of Paradigm-Based Diagnosis and Physician's Diagnosis

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• Each of 430 subjects received a diagnosis using two independent methods: a test-based quantitative paradigm and a semistructured neurological examination by a physician. The paradigm diagnosis was based on a battery of tests that assessed short- and long-term verbal memory and short-term nonverbal memory, orientation, construction, abstract reasoning, and language. The subjects came from a community in Manhattan County, in New York City, and were characterized by diversity with respect to both ethnicity (29.1% black, 33.4% Hispanic) and educational level (23.5% with 6 or fewer years of education, 25.6% college educated). Based on the paradigm, 10.5% of subjects received diagnoses of dementia, 29.1% of cognitive impairment, and 60.5% of normal. Based on the physician's diagnosis, 9.8% were demented, 21.6% cognitively impaired, and 68.6% normal. There was agreement between the two diagnostic methods for 71.8% of subjects. Diagnostic disagreement (n = 121) was in most cases between normal and cognitively impaired (71.0%) or between cognitively impaired and demented (21.5%). There were only nine cases (7.5%) in which a subject was judged demented by one method and normal by the other. The reliability of each method with respect to the other was moderate (intraclass correlation coefficient, .62), while the reliability of a composite diagnosis based on both methods was much higher (.77). The paradigm was more likely than the physician to give the diagnosis of dementia to patients with low educational levels. The physician's diagnosis was strongly influenced by measures of functioning and by the mental status test administered in the semistructured neurological examination. Race and diagnosis were not related when the effect of education was controlled. Strengths and potential weaknesses of each method of diagnosis, and the relationship between education and diagnosis, are discussed.

(*Arch Neurol.* 1992;49:461-467)

An effective quantitative method for the diagnosis of dementia has been described by Stern and his colleagues in the preceding study.[1] Their method applies an explicit, standardized set of decision rules to the results of a complete neuropsychological battery to arrive at a diagnosis.

See also p 453.

To be sure, there are a number of potential disadvantages to the diagnosis of dementia based on a quantitative paradigm. First, due to its inflexible nature, the paradigm may generate incorrect diagnoses because of its inability to accommodate anomalous conditions. For example, a subject who is intimidated by testing procedures mistakenly may be labeled demented by a score-driven paradigm. Second, it would be extremely difficult to develop a paradigm that simulated the judgment of an experienced clinician, who can assess the weight a particular test score or reported symptom should be given, based on the unique characteristics of a particular subject.

At the same time, the use of a quantitative, paradigm-based diagnosis offers several important advantages. First, it ensures a high level of consistency in diagnostic criteria. Second, for many disorders that must be diagnosed primarily on the basis of behavioral criteria, a quantitative, "actuarial" approach to diagnosis has proved superior, in terms of reliability, to diagnosis based on clinical judgment alone.[2]

However, before a paradigm-based diagnosis can be widely adopted, its performance must be directly measured against the traditional method of diagnosis for dementia, rendered by a trained clinician. We report on research in which each subject was given a diagnosis using the paradigm and, independently, by a physician. The subjects were drawn from a densely populated commu-

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nity in New York City characterized by diversity with respect to race, education, language, and national origin. In analyzing data from this sample, the questions we addressed were as follows: (1) To what degree does a paradigm-based diagnosis of dementia agree with a diagnosis based on clinical judgment? (2) What demographic factors and clinical features account for discrepancies between the two diagnostic methods? The ultimate aim of this research is to ensure a high degree of accuracy and consistency in the diagnosis of dementia in heterogeneous populations.

SUBJECTS AND METHODS

Subjects

Subjects were selected from volunteers participating in the Washington Heights–Inwood and Columbia Aging Project. The sample used for this research is described in the preceding article.[1]

Diagnostic Methods

At the time of entry into the Washington Heights–Inwood and Columbia Aging Project, the cognitive status of each subject was evaluated by two independent methods: physician's diagnosis and paradigm-based diagnosis. Each method assigned a subject to one of three ordered diagnostic categories: normal, cognitively disordered, or demented. These categories were assigned the quantitative values of 0, 1, and 2, respectively. This three-point ordinal scale provided the basis for assessing consistency between the two diagnostic methods. The decision to rank subjects on a three-point scale rather than a dichotomy was based on our observation that dementia occurs after a progressive deterioration in cognitive functioning from a normal state. Consequently, many persons who manifest cognitive disorder do not meet all conditions required for a diagnosis of dementia. As noted below, criteria for classifying subjects on the three-point scale were clearly defined for both the paradigm and physician.

The physician's diagnosis of each subject was based on a semistructured medical and psychiatric history, a physical and neurological examination, and the short Blessed Information-Memory-Concentration test (BIMC).[3] The physician reviewed three measures of activities of daily living (ADL): the Schwab,[4] a modified Barthel,[5] and the Blessed Functional Activity Scale (BFAS),[3] parts 1 and 2. Using the results of the examination and the three ADL scales, the physician, based on clinical judgment, assigned each subject to one of the three diagnostic categories indicated above.

The second diagnostic method was based on a battery of neuropsychological tests. A diagnostic paradigm, using criterion scores on each test, as well as a pattern of performance across tests, determined the diagnostic category to which each subject was assigned. Based on the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* definition of dementia,[6] in which memory is the key defining feature, a necessary condition for a diagnosis of dementia in the paradigm is poor performance on two of the three memory "areas" assessed: short- and long-term verbal and short-term nonverbal. In addition, performance on at least two of the following areas must fall below criterion scores: orientation, construction, abstract reasoning, and language. Subjects who did not meet the above requirements but who scored below criterion levels on two or more individual tests were classified as cognitively impaired. Details concerning the types of neuropsychological tests used in the paradigm are provided in the preceding article.[1]

Statistical Analysis

The intraclass correlation coefficient (ICC) was chosen as the index of reliability. Following guidelines suggested by Shrout and Fleiss,[7] we selected two forms of ICC. The first form, the Shrout and Fleiss ICC(3,1), is an index of consistency and, in effect, measures the reliability of either single diagnostic method with respect to the other method. If the reliability is found to be high using this approach, say, .85 or higher, then the two diagnostic methods can be used interchangeably. We will refer to this measure of reliability as model A. Second, we calculated the composite reliability of both diagnostic methods using the Shrout and Fleiss ICC(3,k). This approach, which will be referred to as model B, assesses diagnostic reliability when information from both diagnostic methods is pooled to yield a single composite diagnosis. If the reliability of model A is low, then model B can be used to determine if reliability can be improved to an acceptable level by employing a composite diagnosis.

Table 1.—Analysis of Variance of Diagnoses*

Source	*df*	Mean Square
Between subjects (BMS)	429	0.7304
Within subjects (WMS)	430	0.1721
Between methods (JMS)	1	1.6791
Residual (EMS)	429	0.1686
Total	**859**	0.4509

*Calculation of intraclass correlation coefficients: reliability of either single diagnostic method, $(\text{BMS} - \text{EMS})/[\text{BMS} + (k{-}1)\text{EMS}] = (0.7304 - 0.1686)/[0.7304 + (2 - 1)0.1686] = 0.6249$; reliability of composite diagnosis, $(\text{BMS} - \text{EMS})/\text{BMS} = (0.7304 - 0.1686)/0.7304 = 0.7692$.

Calculation of both ICCs is based on a fixed-effects, subject-by–diagnostic method two-way analysis of variance (ANOVA). See Table 1 for sources of variation and for equations used to calculate reliability using models A and B.

To explore the sources of agreement and disagreement between the physician and paradigm, each subject was assigned to one of nine agree-disagree categories based on the unique combination resulting from the two diagnostic methods (eg, normal by physician's diagnosis and normal by paradigm-based diagnosis; normal by physician's diagnosis and cognitively disordered by the paradigm). In addition, each subject was assigned a composite diagnosis resulting from the sum of the values associated with each diagnostic method. For example, a person diagnosed as cognitively disordered (1) by the physician and demented (2) by the paradigm would have a composite diagnosis of $1+2=3$. The composite score ranged from a value of 0 (diagnosis of normal by both methods) to 4 (demented by both methods). However, for all analyses involving the agree-disagree groups or the composite diagnosis, we eliminated the nine subjects for whom there was maximal disagreement between the two diagnoses: demented according to one, normal according to the other (Table 2). These subjects were excluded because (1) the number of subjects in this category was too small for statistical analysis and (2) the complete lack of agreement between the two diagnostic methods for these few subjects represents a set of anomalous findings that yield the most helpful information when examined anecdotally (see the "Results" section).

Subjects in the seven agree-disagree groups were compared on gender, age, years of education, self-reported race, language, BIMC, Schwab, modified Barthel, and BFAS using one-way ANOVA for continuous variables and χ^2 for categorical variables. Subjects in the five composite diagnosis groups were analyzed in the same manner. Three mutually exclusive categories of race-ethnicity were defined: white, not of Spanish/Hispanic origin; black, not of Spanish/Hispanic origin; and Spanish/Hispanic in origin. A modified form of the Barthel was used to determine whether, in the prior month, the subject needed the help or supervision of another person to complete each of nine activities: eating, dressing, bathing, grooming, getting from bed to chair, walking 45 yd, bladder control, bowel control, and getting in or out of a car, bus, or subway. The yes (1) or no (0) responses were summed to form a score ranging between 0 and 9,

Table 2.—Joint Distribution of Physician's Diagnosis and Paradigm Diagnosis*

Paradigm Diagnosis	Physician's Diagnosis: Normal	Cognitive Deficit	Demented	Total
Normal	53.5 (230)	6.5 (28)	0.5 (2)	**60.5 (260)**
Cognitive deficit	13.5 (58)	12.3 (53)	3.3 (14)	**30.2 (130)**
Demented	1.6 (7)	2.8 (12)	6.0 (26)	**9.3 (40)**
Total	**68.6 (295)**	**21.6 (93)**	**9.8 (42)**	**100.0 (430)**

*Values are percent (number).

Table 3.—Analysis of Variance of Agree-Disagree Groups*

Diagnostic Method			Group Means					
Physician	Paradigm	No.	Age (n=421)	Education (n=421)	BIMC (n=389)	BFAS (n=414)	Barthel (n=407)	Schwab (n=342)
Normal	Normal	230	70.9	12.0	2.6	0.3	0.2	93.5
Normal	CD	58	75.2	8.4	3.8	0.9	0.7	87.4
CD	Normal	28	74.3	9.6	4.8	1.1	0.9	84.4
CD	CD	53	75.5	7.2	8.2	1.4	1.2	80.4
CD	Demented	12	77.2	4.5	9.8	2.3	1.3	70.0
Demented	CD	14	80.7	9.5	13.4	2.4	3.0	63.8
Demented	Demented	26	82.4	8.0	17.1	3.2	1.3	66.7
F ratio	...	...	15.9	18.8	88.0	34.1	10.5	18.5

*BIMC indicates short Blessed Information-Memory-Concentration test; BFAS, Blessed Functional Activity Scale; and CD, cognitive deficit. All F ratios, $P<.0001$.

a scale that had high internal consistency (Cronbach's $\alpha=.89$). The BFAS was scored so that functional deficits attributable to physical problems did not contribute to the total score.

Where one-way ANOVA indicated group differences, the least significant difference multiple comparison test was used to determine which groups differed significantly. All analyses were done using SPSS/PC+ 4.0 (SPSS Inc, Chicago, Ill, 1990).

RESULTS

Based on the paradigm, 10.5% of the subjects were given the diagnosis of being demented; 29.1%, cognitively impaired; and 60.5%, normal. Based on the physician's diagnosis, 9.8% were demented; 21.6%, cognitively disordered; and 68.6%, normal. The joint distribution of physician's diagnosis and paradigm-based diagnosis is presented in Table 2. Of the 430 subjects given diagnoses, there was agreement on 309 (71.8%). Of the 121 subjects on whom there was disagreement, 77 (63.6%) were judged more impaired by the paradigm than by the physician; 44 (36.3%) were found more impaired by the physician than by the paradigm. Eighty-six (71.0%) of the 121 subjects on whom there was diagnostic disagreement were found in the normal vs cognitively disordered categories. Of these 86 subjects, 58 (67.4%) were judged normal by the physician but cognitively disordered by the paradigm. Twenty-six (21.5%) of the 121 subjects on whom there was diagnostic disagreement were in the cognitively disordered vs demented categories. In this case, the disagreements were nearly evenly distributed: 12 (46.0%) were judged demented based on the paradigm but cognitively disordered by the physician; 14 (54%) were judged demented by the physician but cognitively disordered based on the paradigm. Maximum disagreement, in which physician and paradigm diagnoses were two positions apart on the three-point scale, occurred with only nine (2%) of the 430 subjects given diagnoses. In seven of these nine subjects, diagnosis was dementia by the paradigm and normal by the physician.

Reliability

The results of the ANOVA and derived ICCs are presented in Table 1. For model A, the measure of reliability of either single diagnosis, moderate consistency was found between physician and paradigm, as indicated by a reliability coefficient of .62. The reliability of the composite diagnosis, calculated in model B, was substantially higher: .77. This is close to the .85 value considered acceptable for clinical tests and is an adequate level of reliability for research purposes.[8]

Agreement and Disagreement Between Diagnostic Methods

A total of seven categories, representing combinations of paradigm and physician diagnoses, were examined (Table 3). Two of these represented disagreement as to whether a subject was normal or cognitively impaired; two reflected disagreement as to whether a subject was demented or cognitively impaired. The remaining three categories represented agreement on dementia, cognitive deficit, and normal status.

With respect to education, subjects for whom there was agreement on a normal diagnosis were significantly better educated than subjects in any of the six other groups. This group had, on average, nearly 2.5 more years of education than subjects in the next most educated group. With respect to disagreement, there was a marked trend in educational level. Within each pair of categories for

Table 4.—Analysis of Variance in Characteristics Associated With Composite Diagnosis*

Composite Diagnosis	Diagnosis Code	No.	Group Means Age (n=421)	Education (n=421)	BIMC (n=389)	BFAS (n=414)	Barthel (n=407)	Schwab (n=342)
Normal	0	230	70.9	12.0	2.6	0.3	0.2	93.5
Mild CD	1	86	74.9	8.8	4.1	0.9	0.8	86.3
CD	2	53	75.5	7.2	8.2	1.4	1.2	80.4
Severe CD	3	26	79.1	7.2	11.5	2.3	2.1	66.8
Demented	4	26	82.4	8.0	17.1	3.2	1.3	66.7
F ratio	. . .	. . .	23.4	24.4	127.6	51.2	13.7	27.4

*Abbreviations are as in Table 3. All F ratios, $P < .0001$.

which there was disagreement, mean educational level was lower in the group judged more impaired by the paradigm. Of particular interest is the pair in which the disagreement was over whether the subject was demented or had a cognitive deficit. For the group in which the paradigm indicated that the subject was demented, while physician diagnosis was of cognitive deficit, the mean educational level was significantly lower than in any other group, 4.5 years. For those with an identical set of discrepant diagnoses, but rated demented by the physician and as having a cognitive deficit by the paradigm, mean educational level was substantially higher: 9.5 years. These findings suggest that the test-based paradigm may be overestimating the level of cognitive impairment in subjects with little formal education.

With respect to mental status, as measured by the BIMC, those judged demented by the physician but cognitively impaired by the paradigm scored significantly higher, ie, more impaired, on the BIMC than subjects judged demented by the paradigm but cognitively impaired by the physician. Although not statistically significant, the same tendency was found in the two groups where the disagreement was normal vs cognitively impaired: those whom the physician judged more impaired tended to score higher on the BIMC. These findings suggest that the physician was more influenced by the BIMC than was the paradigm.

Individual Cases of Maximum Disagreement

As indicated above, there were nine cases in which a subject was judged normal by one method and demented by the other method. In two cases, the subject was demented according to the physician, normal by the paradigm. In both instances the subject performed well on the neuropsychological tests, which are the basis of paradigm diagnosis. In one of the cases, the BFAS was performed poorly, and the physician thought the patient was borderline but eventually decided on a diagnosis of dementia. In the second case, the subject performed poorly on the BIMC, which, as shown above, was highly influential for the physician, and was judged demented by the physician.

In seven cases, the subject was judged demented by the paradigm and normal according to the physician. In one of these cases, the physician concluded that the patient tested poorly due to a psychiatric condition. In three other cases, the patient performed quite well on the BFAS and reported few functional problems, resulting in a diagnosis of normal by the physician. In the three remaining cases, the subject performed somewhat more poorly on the BFAS (a score of 10 or greater), and there were some functional complaints, but the physician believed there was no cognitive change. In all seven cases, these subjects performed very poorly on the neuropsychological battery and were diagnosed demented by the paradigm. Three of these seven had very low levels of education.

These anecdotal findings are consistent with the results of statistical analyses focused on disagreement between diagnoses rendered by the two methods: those with little education tended to be judged more severely by the paradigm, while those who did not perform well on the BIMC and/or who showed evidence of functional deficit tended to be judged more harshly by the physician—even when performance on the neuropsychological battery was acceptable.

Characteristics Associated With Severity of Composite Diagnosis

The composite diagnosis is given as a function of age, education, the BIMC, and three ADL measures in Table 4. The ordered scale of the composite diagnosis, from 0 (agreement that the subject is normal) to 4 (agreement that the subject is demented), reflects increasing severity of cognitive impairment. The agreement categories (composite score, 0, 2, and 4) are identical in Tables 3 and 4, while the four disagreement categories in Table 3 are collapsed into two categories in Table 4.

As shown in Table 4, there was a progressive increase in age with severity of cognitive disorder. Those judged as normal by both methods were significantly younger than subjects in any other group, while those judged as demented by both methods were significantly older. Subjects in each composite diagnostic category also performed as expected in terms of mental status: there was a significant increase in BIMC score (ie, decrease in performance ability) with increasing severity of diagnosis. Similarly, functional capacity, as measured by the BFAS and Schwab, declined with increasing severity of composite diagnosis, from agreement on normal (0) to agreement on dementia (4). The Barthel Index also indicated a decline in functioning with increased severity of composite diagnosis, with the exception that those with a composite diagnosis of severe cognitive disorder were rated more functionally impaired than those subjects judged to be demented. The fact that the composite diagnosis yields results that are consistent with what is known about the relationship among dementia, age, mental status, and functioning indicates that this diagnosis has good construct validity in addition to reliability.

Table 5.—Association of Composite Diagnosis With Demographics*

Composite Diagnosis	Race-Ethnicity			Language		Gender	
	W	B	Hispanic	English	Spanish	M	F
Normal	71.0 (110)	47.5 (56)	44.3 (62)	60.1 (161)	42.6 (55)	53.9 (62)	54.9 (168)
Mild CD	14.8 (23)	28.0 (33)	20.7 (29)	19.8 (53)	21.9 (28)	24.3 (28)	19.0 (58)
CD	5.8 (9)	7.6 (9)	23.6 (33)	6.7 (18)	24.8 (32)	11.3 (13)	13.1 (40)
Severe CD	3.9 (6)	7.6 (9)	5.7 (8)	6.3 (17)	6.2 (8)	3.5 (4)	7.2 (22)
Demented	4.5 (7)	9.3 (11)	5.7 (8)	7.1 (19)	4.7 (6)	7.0 (8)	5.9 (18)

*CD indicates cognitive deficit. Race-ethnicity, $\chi^2=42.95$, $P<.0001$; language, $\chi^2=28.48$, $P<.0001$; and gender, $\chi^2=3.43$, $P<.49$. Values are expressed as percent (number).

However, while educational level differed significantly between the diagnostic groups, there was no clear ordering of educational level with respect to composite diagnosis. For example, those with the most severe composite diagnosis—agreement with respect to dementia—were intermediate with respect to the other groups in terms of education, with a mean of 8 years.

Relationships between composite diagnosis and categorical demographic variables are given in Table 5. There was a statistically significant relationship between composite diagnosis and race-ethnicity: most striking is the fact that 71% of white subjects but only 47.5% of black subjects and 44.3% of Hispanic subjects were judged to be normal. There was also a significant relationship between diagnosis and the language spoken in the subject's home: as would be expected from the findings with respect to ethnicity, 60.1% of English-speaking subjects but only 42.6% of Spanish-speaking subjects were judged to be normal. There was no relationship between gender and diagnosis.

The strong relationship between ethnicity and diagnosis, a finding that has been reported in previous research as well,[9] was examined further to determine whether a confounding variable, such as age or education, might explain the observed relationship. A one-way ANOVA indicated that the mean educational level for whites (13.0 years) was significantly greater than for either blacks (9.9 years) or Hispanics (7.2 years). An analysis was therefore performed to examine the relationship between race and diagnosis while controlling for the effect of education. The subject's age was also controlled in the analysis because of the strong relationship that exists between age and diagnosis (Table 4).

Two logistic regression models were developed using a dichotomous diagnostic outcome: agreement on normal vs all other diagnoses. In the first model, two indicator variables representing minority status (black, 1, other, 0; and Hispanic, 1, non-Hispanic, 0) were entered. Both race and Spanish origin were significantly related to the outcome ($P<.001$), confirming the results described above, based on the χ^2 statistic. In the second model, age and education, the potential confounding variables, were entered in the first step. As expected, both age and education were significantly related to the outcome ($P<.001$). A forward stepwise selection procedure was then used in an attempt to introduce the minority status variables into this second model. Neither variable was "allowed" to enter, using a .05 probability of a score statistic for variable entry. This indicates that when age and education were statistically controlled, minority status was unrelated to diagnosis. Thus, the tendency to diagnose white subjects as normal at a higher rate than minority subjects appears to reflect the lower educational level of members of minority groups in our study sample, rather than a genuine relationship between race and diagnosis.

Strength of Relationships

Further to assess the strength of relationship between each characteristic and the individual diagnoses, the ANOVAs were repeated separately for the physician and paradigm. In each of these ANOVAs, there were three classification categories: normal, cognitively impaired, and demented. The results are given in Table 6. Because of the moderate agreement between the two diagnostic methods, demographic and other characteristics that were associated with the outcome of one method of diagnosis tended to be associated in the same direction with the other diagnosis. As with the composite diagnosis, the relationship between diagnosis rendered by each method and each of the characteristics examined was highly significant.

However, there were distinct differences between diagnoses with respect to R^2, the proportion of variability in diagnosis that can be accounted for by a key characteristic. Age was related to physician diagnosis about as strongly as to paradigm diagnosis. However, education was more strongly associated with paradigm diagnosis ($R^2=.18$) than with physician diagnosis ($R^2=.11$). Performance on the memory status test (BIMC) was more strongly associated with each type of diagnosis than was any other variable examined. However, the relationship between the BIMC and physician diagnosis ($R^2=.53$) was much stronger than the relationship between BIMC and paradigm diagnosis ($R^2=.37$). Finally, all three measures of functional impairment were more strongly associated with physician diagnosis than with paradigm diagnosis.

In Table 6, the strength of relationship between each key characteristic and the composite diagnosis categories (from Table 3) is also given (row 3). In each case, the relationship between the characteristic and these categories is stronger than for the three categories of each diagnosis taken separately (rows 1 and 2). This is due at least in part to the increased reliability of the composite diagnosis: because there is less error variance associated with the composite than with the individual diagnoses (Table 1), there is more reliable variance available for association with key subject characteristics.

COMMENT

We have used ICC and other procedures to assess the relationship between independent diagnoses rendered by physicians' assessment and neuropsychological testing.

Table 6.—Percent Explained Variance in Diagnosis (R^2)*

Method	Age	Education	BIMC	BFAS	Barthel	Schwab
Paradigm	13.8	17.8	36.6	23.1	7.4	14.9
Physician	14.4	11.2	52.9	29.8	10.2	22.0
Composite	18.4	19.3	57.1	33.3	11.9	24.5

*BIMC indicates short Blessed Information-Memory-Concentration test; BFAS, Blessed Functional Activity Scale.

One purpose of this investigation is to establish a method to assess and refine a neuropsychological diagnostic paradigm for cognitive deficit, including dementia. A second goal is to identify strategies for maximizing diagnostic reliability, using appropriate information from both physicians' assessment and neuropsychological testing.

Physician vs Paradigm Diagnosis

In 71.8% of the cases examined, there was diagnostic agreement between the two methods. This level of consistency is reflected in a moderate ICC, using model A (.62). This value may be interpreted as the proportion of reliable variance in either of the diagnostic methods, with respect to the other. From one standpoint, these findings indicate that the current version of paradigm-based diagnosis is not acceptable because it yields results that are not sufficiently consistent with the traditional method used to diagnose cognitive deficit. On the other hand, the reliability obtained between the traditional diagnosis and the current version of the paradigm is high enough to anticipate that further refinement of the paradigm could raise reliability to an acceptable level.

In fact, the level of consistency obtained in the results is probably an underestimate, since subjects who did not represent a challenge for the diagnostician were not included in the study sample. The sample did not include subjects who were too demented to complete one or more of the neuropsychological tests. Had these unambiguously demented subjects been included in the research sample and assigned failing scores on the tests they were unable to complete, the percentage of agreement between physician and paradigm diagnoses, and the value of the ICC for model A, would have been even higher. The fact that level of agreement was so high even in a sample in which the difficulty of rendering an accurate diagnosis was elevated is particularly encouraging.

Reliability of the Composite Diagnosis

When there is at least some consistency (positive correlation) between diagnostic methods, a composite diagnosis will always yield greater reliability than a diagnosis rendered by one method alone.[7] In research, one consideration in deciding between using a single method and a composite diagnosis is whether the "benefit" of the composite diagnosis in terms of increased reliability is worth the additional "cost" of examining each patient using two different and independent diagnostic methods. For our research, we believe that the single diagnosis reliability (model A) is too low and that the increase in reliability of the composite diagnosis (model B) is worth the cost of obtaining two independent diagnoses.

Discrepancies Between Diagnoses

While the composite diagnosis has good reliability and construct validity, one goal of this research effort is to improve the reliability and accuracy of a paradigm-based diagnosis. The analysis of cases in which there were discrepancies between physician's and paradigm-based diagnoses yielded two related findings that suggest possible shortcomings in the current version of the paradigm. First, when there were discrepancies in diagnosis, those with low educational levels tended to be judged more impaired by the paradigm than by the physician. The results also indicate that the educational level of the subject was more strongly associated with paradigm than with physician diagnosis.

In the absence of evidence from postmortem pathological examination, it is not possible to determine on a case-by-case basis which of the discrepant diagnoses is the correct one. It might be argued that the paradigm tends to overdiagnose dementia among those with little formal education, and that this shortcoming is particularly problematic in samples like ours, which contains a substantial number of subjects with little or no formal education. It would be expected, according to this argument, that subjects who have no organically based cognitive deficit, but who lack rudimentary test-taking skills, tend to perform poorly on the neuropsychological tests, and that some would obtain scores low enough to meet paradigm-based criteria for cognitive deficit or even dementia. When the diagnosis is made by a physician, on the other hand, the subject's educational level can be weighed in making a final determination of cognitive status. A quantitative method for adjusting the paradigm score for educational level is presented in an accompanying study.

A relationship between low educational level and the diagnosis of dementia or cognitive deficit has been observed in previous research.[10-13] However, several investigators have pointed out that no findings to date have ruled out the possibility that rates of dementia are truly higher among those with little or no education than among the better educated.[14,15] Also, it is important to note that the physician as well as the paradigm tended to rate as demented or as having a cognitive deficit a disproportionately large number of subjects with little or no education. Thus, the only firm conclusions that can be drawn from the observed disparities between physician and paradigm diagnosis are (1) that those with low educational levels are more likely to be given diagnoses of dementia; (2) that there is a stronger association between paradigm diagnosis and education than between physician diagnosis and education; and (3) that there is clearly a need for further research focused on the assessment of dementia among subjects with little or no formal education. A second source of disparity between physician and paradigm diagnoses is the functional capacity of the subject. The version of the paradigm used in this research included no measures of the subject's day-to-day functional capabilities. Physicians, on the other hand, had access to three ADL measures. The findings we obtained indicate that physicians were incorporating information about functioning in making a final diagnosis: subjects rated more cognitively impaired by the physician than by the paradigm evidenced poor functioning on all three measures, and all measures of functional assessment were more closely associated with physician diagnosis than with paradigm diagnosis. This interpretation is consistent with findings reported in the preceding article.[1]

The analysis of the cases in which there were discrepant diagnoses also suggests that physicians were strongly influenced by the BIMC, the mental status test administered in the semistructured interview on which the physician's diagnosis was based. Among those subjects judged demented by the physician but as having a cognitive disorder by the paradigm, the BIMC score was worse (mean, 13.4) than among those subjects judged demented by the paradigm but as having a cognitive disorder by the physician (mean, 9.8). Moreover, the association between BIMC score and diagnosis, as measured by R^2, is much stronger for the physician than for the paradigm (Table 6). Finally, the finding of a strong influence of the BIMC on physician diagnosis suggests a possible deficiency with respect to this method of diagnosis. Since the BIMC is the only mental status test administered in the semistructured examination, it is understandable that the subject's performance on this test would be a key factor in the physician's diagnosis. On the other hand, performance on the BIMC is not always indicative of performance on the full battery of neuropsychological tests required for a paradigm diagnosis, as indicated in the analysis of the two cases in which the physician indicated the subject was demented and the paradigm determined the subject was normal. The neuropsychological tests, which are not part of the semistructured examination, measure a broad range of cognitive abilities. A physician's diagnosis may be too dependent on the results of a single mental status test.

Conclusions

Taking the results presented herein together with the findings described in the preceding article, there is good reason to believe that a modified version of a paradigm-based diagnosis for cognitive deficit and dementia would be a viable tool for diagnosing dementia in a heterogeneous population. Reliability, and probably the validity of the paradigm, could be improved by adding one or more measures of function to the battery of neuropsychological tests. The results also suggest that the physician's diagnosis might be improved by using additional tests of cognitive performance in the semistructured examination.

However, using the two methods as they are currently defined, reliability will be maximized when a paradigm-based diagnosis is used in conjunction with, rather than instead of, a physician's diagnosis. The strength of the current paradigm lies in the comprehensive quantitative measurement of cognitive status in the neuropsychological battery. A physician's diagnosis is valuable because functional measures are considered, and because there appears to be at least some adjustment made for the educational level of the subject. In creating a composite diagnosis, the strength of each method is utilized and the impact of each method's weaknesses is attenuated.

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Original Contribution

Evoked Potentials in Cerebrotendinous Xanthomatosis and Effect Induced by Chenodeoxycholic Acid

Mauro Mondelli, MD; Alessandro Rossi, MD; Chiara Scarpini, MD; Maria Teresa Dotti, MD; Antonio Federico, MD

• Evoked potentials are reported in 10 patients with cerebrotendinous xanthomatosis, eight of whom had peripheral neuropathy. Four subjects showed delayed N13 to N20 interpeak latencies for arm somatosensory evoked potentials, and five showed moderately prolonged I to III and I to V interpeak latencies of brain-stem auditory evoked potentials. Six of seven patients showed marked delay and desynchronization of visual evoked potentials. All five patients undergoing transcutaneous magnetic stimulation of the motor cortex presented greatly delayed central motor conduction time, especially of the lower limbs. After treatment with chenodiol (750 mg/d for at least 2 years), there was a significant improvement in nerve conduction velocities, N13 to N20 interpeak latencies, and visual evoked potential latencies. Brain-stem auditory evoked potentials remained unchanged.

(*Arch Neurol.* 1992;49:469-475)

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive neurometabolic disease involving lipid metabolism. The major clinical features, usually manifesting before 20 years of age, include tendon xanthomas, cataract, cerebellar ataxia, pyramidal tract signs, peripheral neuropathy, mental deterioration, and psychiatric disorders. The disease is caused by defective bile acid synthesis characterized by an absence of chenodeoxycholic acid in the bile and a marked increase in cholestanol in the plasma and many tissues.[1-3]

Although peripheral neuropathy has been extensively reported in CTX,[4-9] few electrophysiological data on the central nervous system have been available up to now.[10,11] In this study, we report evoked potential (EP) findings in 10 patients with CTX and the effect of chenodiol treatment in seven of these patients.

PATIENTS AND METHODS

Ten patients with CTX were studied. Diagnosis was based on the clinical data (Table 1) and on high plasma levels of cholestanol (Table 2). Detailed clinical findings in the patients have been reported elsewhere.[12]

An electrophysiological study of the peripheral nervous system was performed in all patients, including standard needle electromyography of brachial biceps and tibialis anterior muscles; motor conduction velocity (MCV), distal motor latency (DML), and compound muscle action potential amplitude (CMAPa) of median, ulnar, deep peroneal, and tibial nerves; and sensory conduction velocity (SCV) and sensory action potential amplitude (SAPa) of median, ulnar, superficial peroneal, and sural nerves. Details of the method, summarized in Fig 1, have already been published.[13]

Short-latency somatosensory EPs (SEPs) were obtained by independent stimulation of the left and right median nerve at the wrist. Brain-stem auditory EPs (BAEPs), preceded by pure-tone audiometry, were elicited by monaural alternate-click stimulation. Visual EPs (VEPs) were obtained, after visual acuity test, with a black-and-white checkerboard pattern stimulator with independent stimulation of each eye in seven patients (Nos. 1, 2, 5, 6, 7, 9, and 10). The details of EP methods, summarized in Figs 2 through 4, have been published elsewhere.[14,15]

Motor EPs (MEPs) were obtained by transcutaneous magnetic stimulation of the motor cortex and recording from the thenar eminence and abductor hallucis contralateral to the stimulated side. Stimulation intensity was kept 50% above the threshold value, and recordings were acquired during a slight tonic voluntary contraction of at least 5% maximal isometric tension of the test muscle. Eight to 12 recordings were obtained for each side, and the shortest motor latency was considered. Central motor conduction time (CMCT) was calculated by the method of minimal "f" wave (of 20), according to the following formula[16]: $\mathrm{CMCT} = \mathrm{MEP} - [(\mathrm{f\ wave} - \mathrm{DML} - 1)/2 + \mathrm{DML}]$. All evoked responses were considered abnormal if they were 2.5 SDs above or below the mean control values.

Seven patients (Nos. 1, 2, 4, 6, 7, 8, and 10) were treated with oral chenodiol (750 mg/d) according to the protocol of Berginer et al.[17] They did not receive any other drugs, except anticonvulsants. In six patients (Nos. 1, 2, 4, 6, 8, and 10), nerve conduction velocities (NCVs), BAEPs, and cholestanol plasma levels were checked after 2 and 4 months of treatment. After 2 years of therapy, NCVs, SEPs, BAEPs, and VEPs were checked again in five patients (Nos. 1, 2, 6, 7, and 10); subject 4 died in a car accident, and patient 8 did not report for follow-up after 2 years. On this occasion, MEPs were also obtained in these five subjects.

The differences between the neurophysiological measures before and at different times after therapy, and between pretreated subjects and 30 controls of the same age, were analyzed by nonparametric tests: the sign test for paired data and the Mann-Whitney *U* test for unpaired data.

RESULTS

All patients showed a moderate chronic neurogenic pattern (enlargement of motor unit potentials and reduc-

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Table 1.—Clinical Findings in 10 Patients With Cerebrotendinous Xanthomatosis

	Patient No./Age, y/Sex*									
	1/32/F	2/34/F	3/36/F	4/26/M	5/38/F	6/37/F	7/29/M	8/44/F	9/44/M	10/31/M
Age at onset of disease, y	10	13	10	8	10	8	22	20	30	8
Tendon xanthomas	+	+	+	+	+	+	+	+	+	+
Cataract	+	+	+	+	+	+	+	+	−†	+
Cerebellar signs	+	−	−	+	+	−	+	+	+	+
Spastic paraparesis	−	−	−	−	−	+	+	+	+	+
Babinski's sign	−	−	−	−	+	−	−	+	+	+
Extrapyramidal sign	−	−	+	−	−	−	−	+	−	−
Deep reflexes	−			−						
Mental deterioration	+	+	+	+	+	+	+	+	+	−
Psychiatric symptoms	−	+	+	+	+	−	+	−	+	+
Seizures	+	−	+	+	−	−	+	−‡	−	−

*Plus sign indicates present; minus sign, absent; downward arrow, depressed; and upward arrow, hyperactive.
†Opacity of crystalline lens.
‡Febrile seizures.

Table 2.—Plasma Sterol Concentrations

Patient No.	Cholestanol, mmol/L	Cholesterol, mmol/L
1	0.08	3.52
2	0.09	3.47
3	0.06	2.36
4	0.07	3.03
5	0.09	4.70
6	0.07	4.86
7	0.06	2.43
8	0.04	4.52
9	0.05	2.90
10	1.00	4.14
Controls	<0.03	<6.46

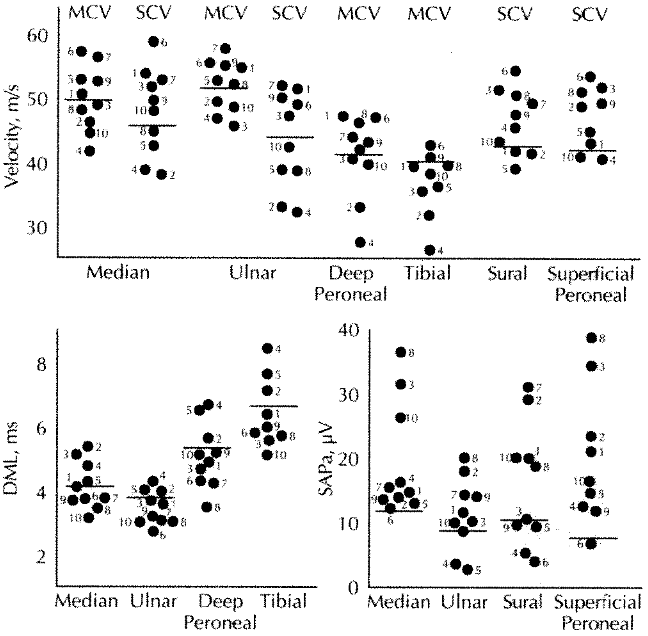

Fig 1.—*Motor conduction velocity (MCV) values of median and ulnar (from the elbow to the wrist), deep peroneal (from the capitulum fibulae to the ankle), and tibial nerves (from the popliteal fossa to the medial malleolus), and sensory conduction velocity (SCV) values of median (from the third finger to the wrist), ulnar (from the fifth finger to the wrist), sural (from the sura to the lateral malleolus), and superficial peroneal nerves (from the inferior third of the leg to the ankle); distal motor latency (DML) values determined with a distance of 7 cm between the stimulating and recording points for median and ulnar nerves, 9 cm for the deep peroneal nerve, and 13 cm for the tibial nerve; and sensory action potential amplitude (SAPa) calculated peak to peak. Skin temperature was kept between 32°C and 35°C.*

tion of recruitment patterns at full effort) on electromyographic examination. A reduction of MCVs and SCVs was found in eight subjects, in at least three nerves in six of them. In six cases, DMLs were prolonged in at least one nerve. Patient 6 showed only a reduction in SAPas, and no peripheral changes were observed in case 7 (Fig 1). Compound muscle action potential amplitudes were normal in all subjects; a slight reduction was observed only in the median and tibial nerves of patient 4.

Table 3 gives SEP, BAEP, and VEP results. In five subjects, the absolute latency of the N9 component was increased. The N13 to N20 interpeak latencies (IPLs) were prolonged in four cases, while N9 to N13 IPLs were normal in all. Almost symmetrical BAEP changes consisted of I to V IPL delays in five patients, coupled in four cases with an increase in I to III IPLs. These changes were relatively moderate and ranged between +2.8 and +3.7 SDs of the mean of controls. The III to V intervals, configuration of BAEP waves, and pure-tone audiometry results were normal in all cases. The VEPs were delayed and temporally dispersed in six of seven patients. Their visual acuity ranged between 3/10 and 7/10 OU. Fundus oculi were normal in all. In subjects 1 through 8, lenses were removed, but lenses were not removed in any subjects after starting treatment with chenodiol. The MEP latencies were abnormal in all five subjects studied (four of them had peripheral neuropathy), but the estimation of CMCT showed a marked delay, especially for the lower limbs (Table 4).

There were significant differences between pretreated subjects and controls in all EP findings ($P<.001$) except for N9 to N13 and III to V IPLs (not significant), in MCVs of

Table 3.—IPLs and Amplitudes*

Patient No.		BAEPs			SEPs			VEPs		
		I-III	III-V	I-V	N9	N9-N13	N13-N20	P2	N1-N2	Amp
1	R	2.48†	1.96	4.44†	9.84	3.36	6.1	128†	92†	2.2†
	L	2.52†	2.00	4.52†	9.72	4.08	5.2	136†	88†	2.9†
2	R	2.28	1.76	4.04	10.40†	3.50	6.3	116†	90†	4.1
	L	2.24	1.88	4.12	9.84	3.56	6.4	114†	94†	5.8
3	R	2.44†	2.00	4.44†	10.40†	4.10	5.4	. . .	. . .	. . .
	L	2.36	1.92	4.28	9.84	4.26	5.9	. . .	. . .	. . .
4	R	2.12	1.80	3.92	11.70†	4.00	5.3	. . .	. . .	. . .
	L	2.24	2.00	4.24	12.10†	3.70	5.8	. . .	. . .	. . .
5	R	2.00	1.72	3.72	9.96	3.04	7.6†	128†	110†	3.0†
	L	1.88	2.08	3.96	9.36	3.44	6.8†	136†	108†	2.6†
6	R	2.16	1.88	4.04	9.12	3.58	7.4†	128†	100†	4.1
	L	2.12	2.00	4.12	8.76	4.14	7.0†	134†	112†	5.7
7	R	2.28	1.80	4.08	9.84	3.56	5.9	124†	88†	3.7
	L	2.32	1.96	4.28	10.00	3.90	6.0	128†	86†	5.4
8	R	2.56†	2.04	4.60†	9.84	3.36	6.3	. . .	. . .	. . .
	L	2.48†	2.08	4.56†	9.36	3.54	6.9†	. . .	. . .	. . .
9	R	2.28	2.04	4.32	11.00†	3.80	6.9†	118†	110†	6.8
	L	2.52†	2.12	4.64†	11.50†	3.80	7.2†	112†	104†	3.9
10	R	2.24	2.20	4.44†	11.60†	4.30	6.0	100	86†	10.0
	L	2.40	2.04	4.44†	11.20†	4.10	5.9	95	82	9.1

*IPL indicates interpeak latency (milliseconds); BAEP, brain-stem auditory evoked potential; SEP, somatosensory evoked potential; VEP, visual evoked potential; and Amp, amplitude (in microvolts). The age of controls for SEP determinations ranged from 15 to 60 years. N9 normal values were corrected for height. The controls for BAEP and VEP determinations were matched for sex and age.

†Value 2.5 SDs above or below the mean of controls.

Table 4.—MEP Findings*

Patient No.		Thenar Eminence				Abductor Hallucis			
		MEP	f Wave	DML	CMCT	MEP	f Wave	DML	CMCT
1	R	23.7	26.2	2.64	9.78†	45.2	50.2	5.72	17.74
	L	23.2	26.4	3.20	8.90†	46.3	49.6	5.64	19.18†
2	R	22.8	24.8	3.34	9.23†	48.8	48.4	5.90	22.15†
	L	22.0	25.5	3.42	8.04	49.4	48.6	5.88	22.66†
6	R	23.3	24.2	4.08	9.66†	45.2	45.6	6.16	19.82†
	L	25.35	25.8	4.20	10.85†	48.6	48.8	6.72	21.34†
7	R	28.0	26.6	3.36	11.88†	52.0	53.6	7.08	22.16†
	L	31.35	26.0	3.52	13.94†	47.2	50.0	7.80	18.80†
10	R	27.4	28.8	3.84	11.58†	54.4	53.6	5.96	25.12†
	L	25.3	28.2	3.12	10.14†	55.4	50.4	5.76	27.82†
Control, mean±SD		19.50±1.61	. . .	. . .	5.55±1.13	39.27±3.44	. . .	. . .	13.40±1.81

*MEP indicates motor evoked potential; DML, distal motor latency; and CMCT, central motor conduction time. Findings were by magnetic stimulation of motor cortex and electrical stimulation of median and tibial nerves.

†Value 2.5 SDs above the control mean.

all nerves ($P<.001$), in DMLs of median and tibial nerves ($P<.001$), in DMLs of ulnar and deep peroneal nerves ($P<.01$), in SCVs of median ($P<.01$) and of other nerves ($P<.05$), and in SAPas of sural and superficial peroneal nerves ($P<.05$). There were no significant differences in SAPas of ulnar and median nerves and in CMAPas of all nerves.

Figures 5 through 7 show the effect of chenodiol treatment. A significant decrease ($P<.05$) in cholestanol plasma levels was already evident after 2 months of therapy with chenodiol (Fig 6), together with recovery of almost all NCVs and DMLs (Fig 5); this was more evident after 4 and 24 months. No statistical modifications were noted for SAPas, CMAPas, BAEP IPLs, and N9 to N13 intervals. A significant improvement in N9 ($P<.05$), N13 to N20 ($P<.05$), and P2 latencies ($P<.01$) after 2 years was observed (Figs 5 and 7).

Figures 2 through 4 demonstrate BAEPs in patient 1,

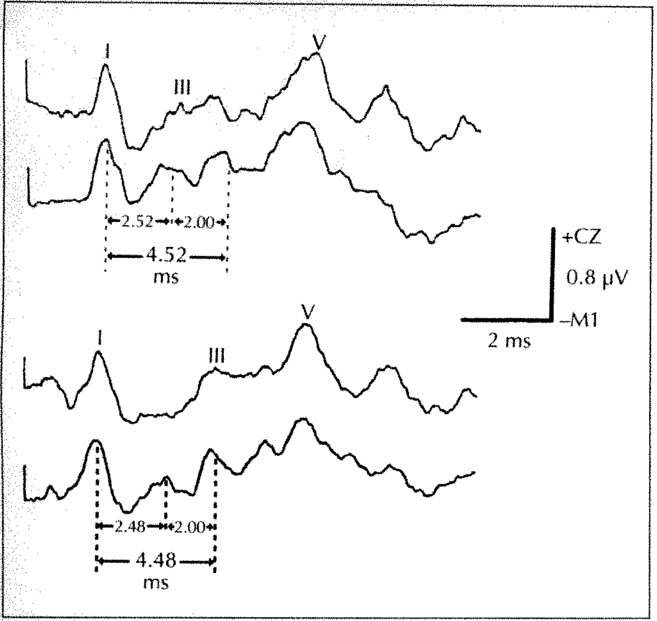

Fig 2.—*Brain-stem auditory evoked potentials of subject 1 to left ear stimulation (frequency, 10 Hz; intensity, 65 dB above perceptive threshold and 45 dB white noise masking the other ear) before treatment (top) and after 2 years of therapy (bottom). Two averaged responses (1024 stimuli) were filtered (bandpass, 3 to 3000 Hz) and superimposed for each recording. The I to III and I to V interpeak latencies were moderately prolonged and remained unchanged after 2 years of therapy.*

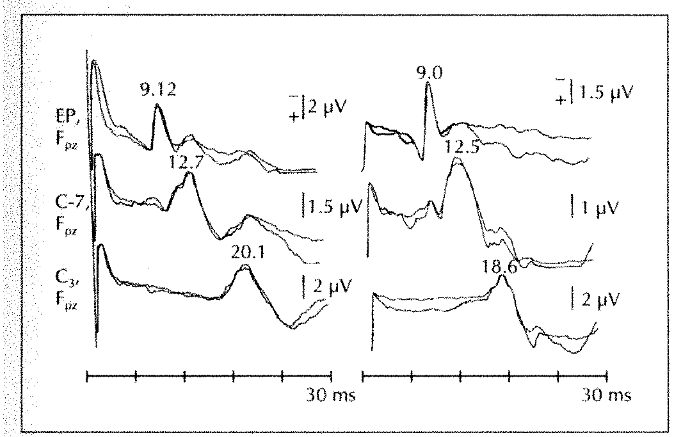

Fig 3.—*Somatosensory evoked potentials of subject 6 to right median nerve stimulation at the wrist at 3 Hz before treatment (left) and after 2 years of therapy (right). Two averaged responses (1024 stimuli) were filtered (bandpass, 1 to 6000 Hz) and superimposed for each recording. The N9 to N13 interpeak latencies (IPLs) were normal; the N13 to N20 IPL was delayed (7.4 milliseconds) before therapy and improved after 2 years of treatment (6.1 milliseconds). EP indicates Erb's point.*

SEPs in patient 6, and VEPs in patient 7, respectively, before and after treatment. Figure 8 shows the motor response to magnetic cortical stimulation in the thenar eminence and abductor hallucis muscles of case 7.

COMMENT

All 10 of our patients showed clinical and biochemical manifestations of CTX. In eight of them there was electrophysiological evidence of moderate motor and sensory neuropathy. A chronic neurogenic pattern on electromyography, decreased SCVs and MCVs, delayed DMLs, and normal or slightly reduced SAPas and CMAPas suggested a demyelinating neuropathy. Nevertheless, clinical evidence of a slight peripheral neuropathy was present in only four cases. In the remaining six cases, with severe pyramidal signs, clinical expression of peripheral damage was scarce. Peripheral neuropathy already has been reported in CTX.[6,10,18] Histological findings reported in the literature were not homogeneous and showed demyelination and remyelination processes,[4,7] primary axonal degeneration,[8] or both,[9] or compressive and/or ischemic changes.[5] Our data confirm the high incidence of peripheral neuropathy in CTX.

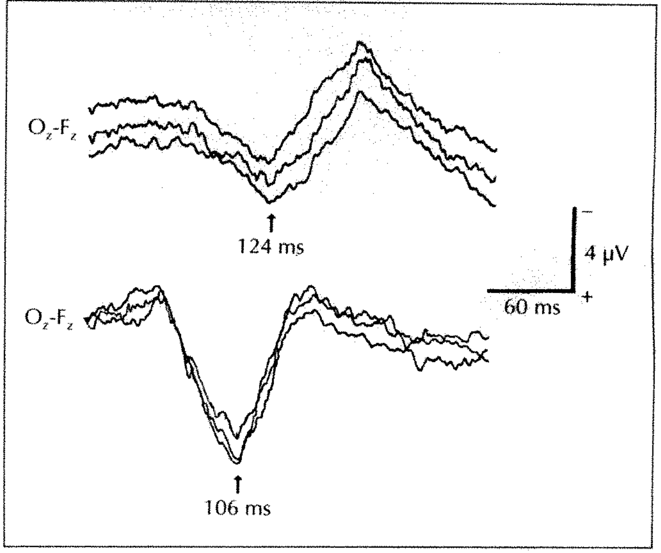

Fig 4.—*Visual evoked potentials of subject 7 to right eye stimulation (at 1 Hz, cheks 30′, contrast 75%) before treatment (top) and after 2 years of therapy (bottom). Two averaged responses (256 stimuli) were filtered (bandpass, 1 to 250 Hz) and superimposed for each recording. Basal P2 latency was delayed (124 milliseconds) but markedly improved after treatment (106 milliseconds).*

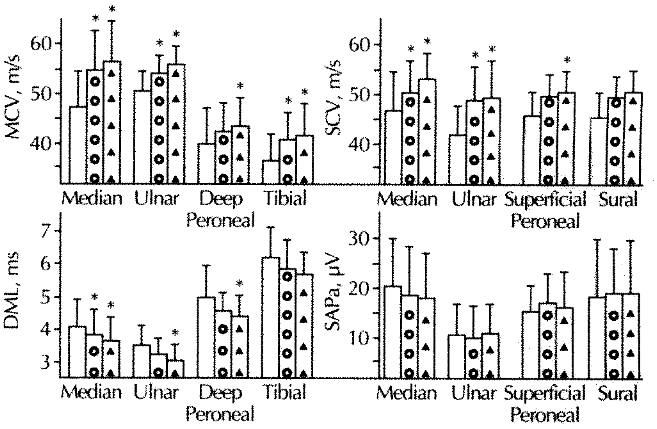

Fig 5.—*Mean (±SD) nerve conduction velocities of six patients (Nos. 1, 2, 4, 6, 8, and 10) at different times (before treatment [empty columns]; after 2 months [columns with circles]; and after 4 months [columns with triangles]). MCV indicates motor conduction velocity; SCV, sensory conduction velocity; DML, distal motor latency; SAPa, sensory action potential amplitude; and asterisk,* $P<.05$.

Few data on EPs are available in the literature. Pedley et al[10] described a patient with abnormal SEPs, BAEPs, and VEPs, Katz et al[5] another with BAEP and VEP changes, and Pop et al[8] four cases with late cervical responses to SEPs and delayed P100 latency. Voiculescu

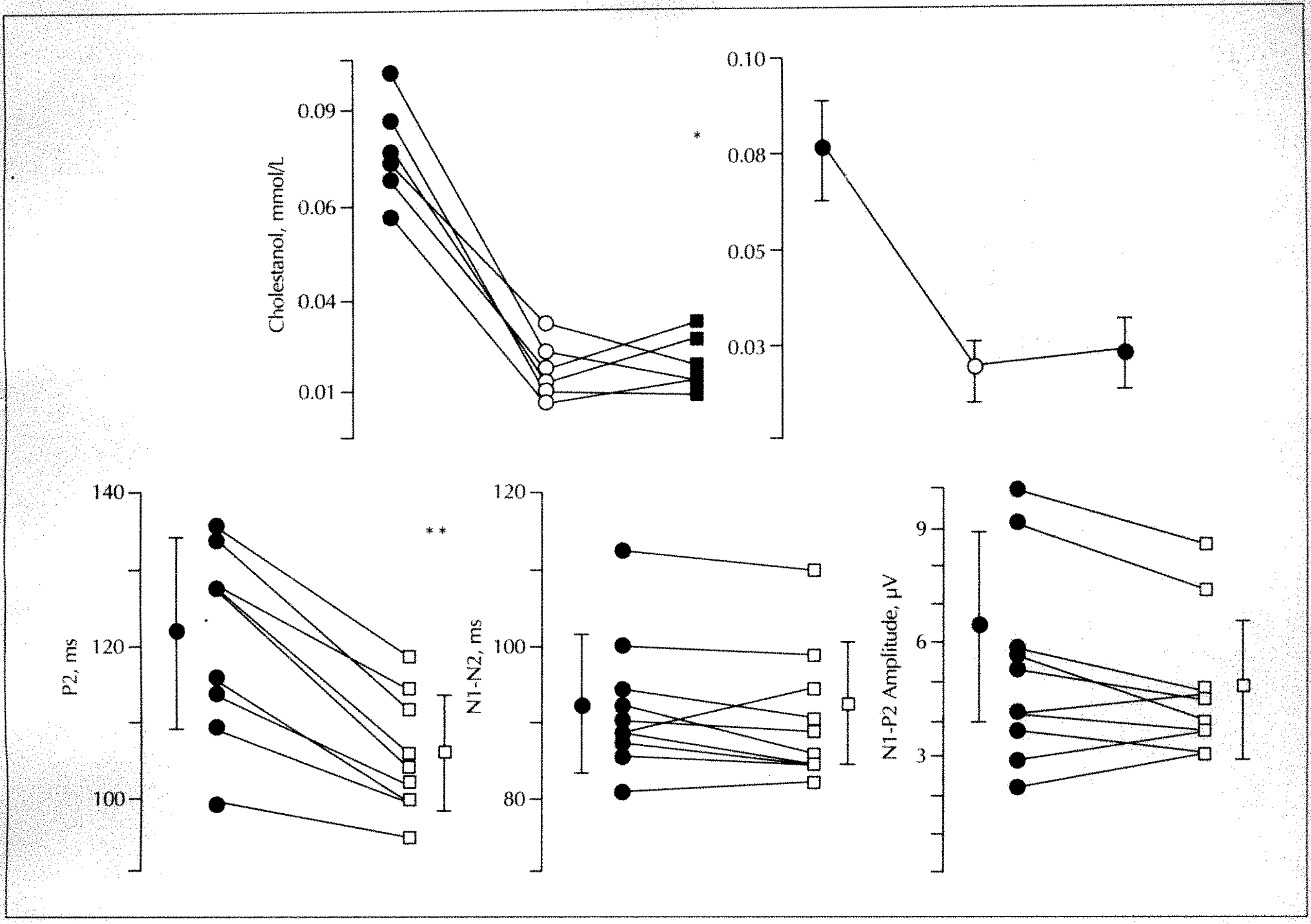

Fig 6.—*Single values, means, and SDs of cholestanol and visual evoked potential findings at different times (before treatment [closed circles]; after 2 months [open circles]; after 4 months [closed squares]; and after 24 months [open squares]). Asterisk indicates* $P<.05$; *double asterisks,* $P<.01$.

et al[9] reported BAEP alterations in one case. Three of four cases reported by Ugawa et al[11] showed delayed sensory and motor (central conduction time), and MEPs were obtained by transcutaneous electrical stimulation of the scalp.

Our study demonstrated a high incidence of EP alterations in CTX. All patients had at least two abnormal EPs, and the most marked and frequent anomalies concerned VEPs and MEPs. Delay and temporal dispersion of VEPs recorded over all leads (O_1, O_z, and O_2) were presumably compatible with increased conduction along the optic nerve. It is unlikely that P2 delay could be caused by cataract. In fact, lens opacity produces latency shift only when cataract is dense and visual acuity is very reduced (<20/200), while P2 amplitude decrease is more constant.[19] In five of seven subjects who underwent VEP study, lenses were removed, and in the other two the cataract was not very dense; visual acuity was not under 3/10 in all cases. Moreover, the reduction of P2 latency observed after treatment was neither coupled to evident clinical improvement of cataract in patient 10 nor to improvement in vision in any patient. None had clinical signs or history suggestive of optic neuropathy. The MEPs showed a prolongation of central conduction time along fast motor myelinated fibers, especially those projecting to the lower limbs. This delay was present in all five patients studied, despite the fact that they had been receiving chenodiol for 2 years. Only three of them had clinical evidence of pyramidal dysfunction. These data are in agreement with neuropathological observations of demyelination of the corticospinal tract.[8] In 50% of cases, SEPs showed delayed N9 compatible with peripheral neuropathy and, in four cases, prolonged central conduction time with normal N9 to N13 IPL. Fifty percent of patients showed moderate I to III and I to V IPL prolongation with normal III to V intervals, in the absence of middle-ear diseases, hearing problems, and abnormalities of tonal audiometry. These data suggest delayed conduction along the acoustic nerve with normal intra-axial acoustic pathways (III to V IPLs were normal), as found in acoustic neuromas,[20] Ramsay Hunt syndrome,[21] Friedreich's ataxia,[22] and Leber's disease.[15] Therefore, EPs could be important in detecting subclinical damage in CTX, as in many other diseases.

The pathogenesis of the disease is linked to defective synthesis of bile acid with an absence of bile chenodeoxycholic acid and a marked increase in cholestanol levels in plasma and certain tissues. In the nervous system, cholestanol may replace cholesterol in the synthesis of central and peripheral nerve myelin, thus impairing conduction. Chenodiol treatment inhibits abnormal endogenous bile acid synthesis, markedly reducing plasma cholestanol levels. Berginer et al[17] demonstrated a significant improvement in clinical, electroencephalographic, and computed tomographic findings in 17 subjects with CTX receiving chenodiol for at least 1 year. Although a

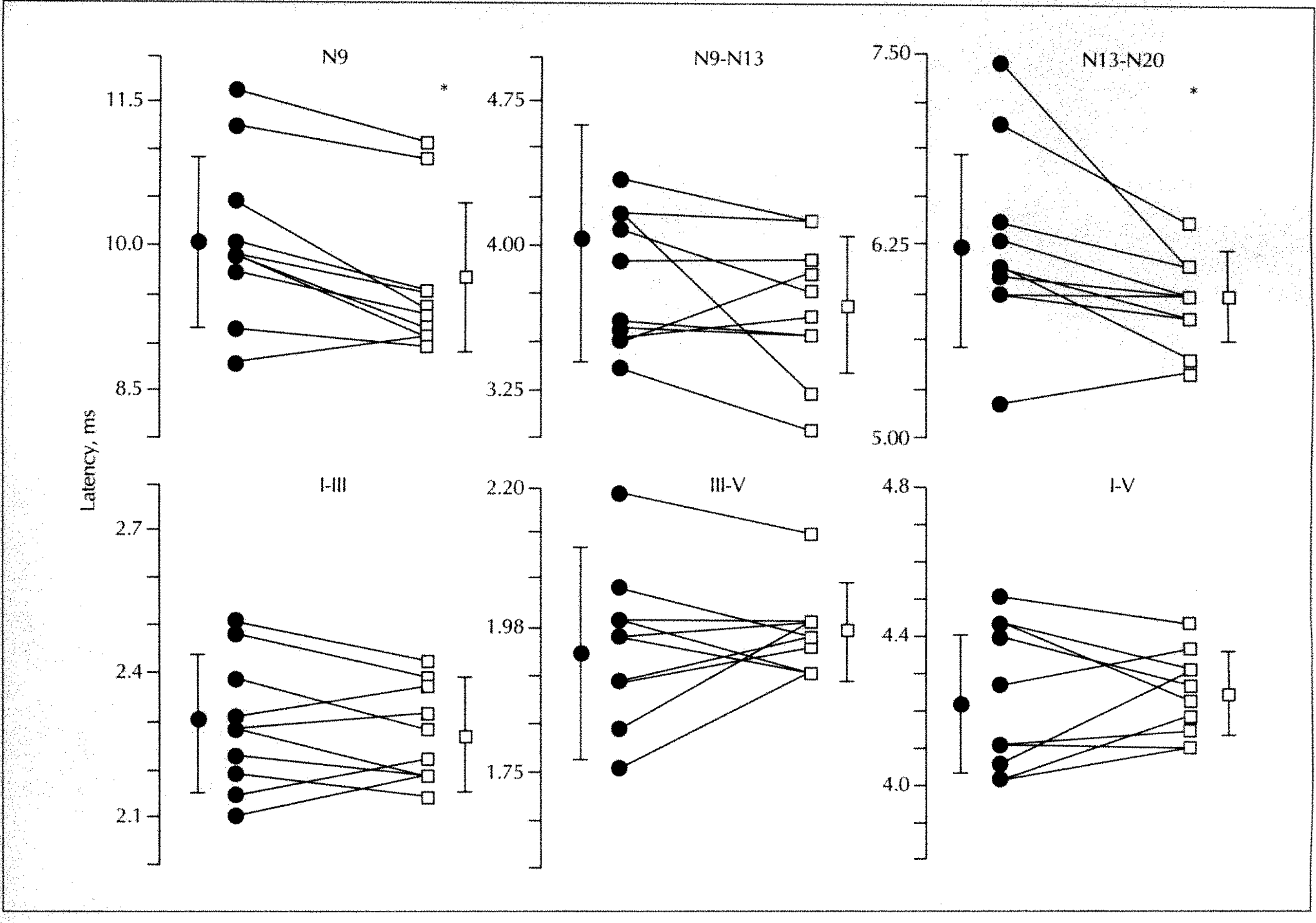

Fig 7.—*Single values, means, and SDs of somatosensory evoked potential and brain-stem evoked potential findings (before treatment [circles]; after 24 months of therapy [squares]). Asterisk indicates $P<.05$.*

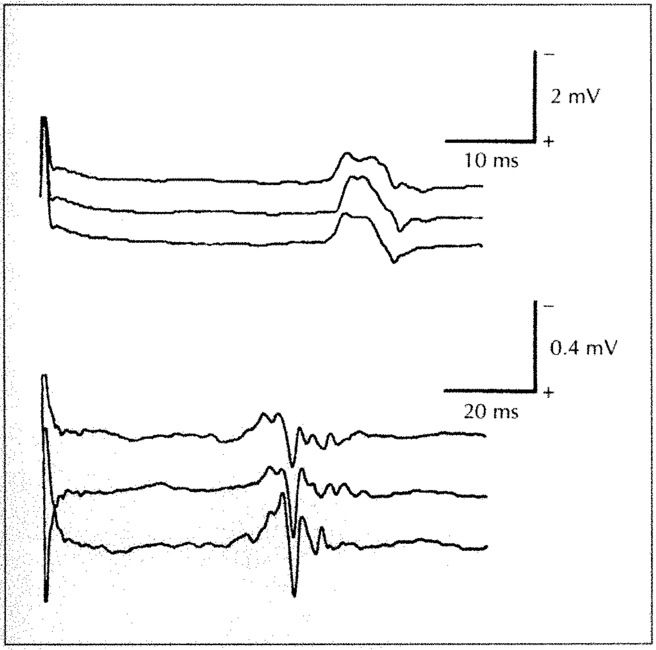

Fig 8.—*Motor evoked potentials (MEPs) of subject 7 to magnetic stimulation of right motor cortex and recording from thenar eminence (top) and abductor hallucis (bottom). The MEPs were prolonged (31.35 milliseconds for upper limb and 47.2 for lower limb). Central motor conduction time, calculated by the "f" wave method, showed a marked delay.*

normalization of NCVs was described by Waterreus et al[18] in six of 11 patients with CTX with peripheral neuropathy, no details were reported regarding the changes' time course and relation to therapy.

There are few data about the effect on EPs. Only Pedley et al[10] have reported a case in which there was marked recovery of VEP latencies to normal values and a moderate improvement in leg SEPs and BAEPs, with unchanged abnormal NCVs and arm SEPs. In our patients, a clear improvement in NCVs in six cases was evident after 2 months of treatment; this was more evident after 4 months, and in the five subjects reexamined after 2 years further improvement was observed. The VEP latencies returned nearly to normal in all subjects. While cataract remained unchanged in the patient (No. 10) who still had crystalline lenses, vision also did not recover. Sensory CCT also improved. The BAEPs were unmodified, but their starting values were normal or nearly normal. Improvements of psychiatric symptoms and, transitorily, of gait disturbances were noted in some patients after treatment, while pyramidal and extrapyramidal signs, mental deterioration, and size of xanthomas remained unchanged. Further electrophysiological and clinical improvements related to therapy could be expected after more prolonged treatment.

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Decline in Cognitive Performance in Aging Twins

Heritability and Biobehavioral Predictors From the National Heart, Lung, and Blood Institute Twin Study

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• The present study examined the contribution of genetic factors to Digit Symbol performance and its decline in 23 monozygotic twin pairs (mean age at examination 1, 57.1 years) and 21 dizygotic twin pairs (mean age at examination 1, 56.3 years). These men were assessed twice during a 5-year interval as part of the National Heart, Lung, and Blood Institute Twin Study. The prevalence of decline (a change, >1 SD) during the 5-year interval was 35% and 39% for monozygotic and dizygotic twins, respectively. The pairwise concordance for decline was 45% in monozygotic and 8% in dizygotic twin pairs, suggesting a possible role for genetic factors in the decline in Digit Symbol performance in this sample. A comparison of baseline biologic and behavioral characteristics within monozygotic twin pairs discordant for decline in Digit Symbol performance revealed that decliners had higher initial systolic blood pressures, lower serum cholesterol levels, and lower heart rates than nondecliners.

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Digit Symbol Substitution[1] is the most age sensitive of all the subtests of the Wechsler Adult Intelligence Scale–Revised,[2] and it is also one of the most effective cognitive tests for distinguishing mild Alzheimer-type dementia from healthy aging.[3,4] This brief but complex task assesses several cognitive processes (eg, visual search, visuomotor coordination, and cognitive flexibility) and places a premium on speed of response. Performance on the Digit Symbol subtest has a known genetic component in both young[5] and elderly[6] subjects. Unknown, however, is the extent to which *decline* in Digit Symbol performance in later life is influenced by genetic factors.

An accelerated rate of decline in Digit Symbol performance has been linked to subsequent mortality in a longitudinal aging study.[7] Other studies have shown a relationship between psychomotor speed performance and cardiovascular disease,[8] blood pressure, hypertension, and/or antihypertensive medication,[9-13] smoking,[14] exercise,[15] and Type A behavior.[16] Additional factors that may be related to cognitive function in general include cholesterol and triglyceride values, diabetes mellitus, alcohol consumption, and left ventricular hypertrophy.[17-22] All of the above studies, except one, were done in unrelated individuals and were thus unable to examine these relationships while controlling for genetic and shared environmental effects.

There is an increased need to understand the environmental and genetic contributions to cognitive decline in elderly persons. Knowledge of both effects could (1) help identify people who appear at risk for serious or premature decline by virtue of their genetic makeup and (2) identify environmental factors that heighten the risk beyond that provided by the genetic determinants. Knowledge of gene-environment interactions, in turn, may provide clues for efforts aimed at preventing premature decline.

The purpose of the present study was twofold. The first objective was to determine the presence of a significant genetic component to decline in Digit Symbol performance in a sample of older, male twins who were examined twice, 5 years apart. Second, taking advantage of the twin design, it was possible, for the first time, to investigate the role of cardiovascular disease and its risk factors in decline after controlling for shared environmental and genetic variability.

METHODS

Subjects

The present study was part of a larger investigation of psychologic, demographic, metabolic, cardiorespiratory, anthropometric, and social aspects of coronary heart disease proneness in identical and fraternal twins. Participating twins were white men and American veterans of World War II and/or the Korean conflict. At entry in the period from 1969 to 1973, 514 twin pairs participated in the first clinical examination of the National Heart, Lung, and Blood Institute (Bethesda, Md) Twin Study. Details of the recruiting process, response rate, determination of zygosity, and examination protocol for this study are available elsewhere.[23-26]

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During the 1981 to 1982 period, 792 of the original cohort of 1028 twin subjects returned for a follow-up examination (labeled "examination 1" for this study). Of these, 184 participants at the Los Angeles (Calif) examination center also received a battery of cognitive tests, including the Digit Symbol Substitution subtest. During the 1986 to 1987 period, 622 twins participated in another examination ("examination 2"), during which all subjects, including the Los Angeles twins, received a series of cognitive tests. As part of this most recent examination, cognitive screening tests, including the Digit Symbol subtest, were given to all 622 individuals (mean age, 63 years) who participated in the examination, including 103 returnees to the Los Angeles examination center. The heritability analyses reported herein were conducted on 44 twin pairs (23 monozygotic [MZ] twin pairs—mean age at examination 1, 57.1 years; 21 dizygotic [DZ] twin pairs—mean age at examination 1, 56.3 years) who participated in both the 1981 to 1982 and 1986 to 1987 examinations and for whom Digit Symbol subtest scores were available.

Measures

The Digit Symbol Substitution subtest from the Wechsler Adult Intelligence Scale–Revised was included at each of the two examinations. The task was to copy symbols that were paired with digits; the coding key was visible throughout, thereby reducing demands placed on memory. Standard administration and scoring procedures were followed. The raw score (number of items completed correctly in 90 seconds) at each examination and the change in raw score from the first to second examination (examination 1 – examination 2) were subjected to genetic analysis.

The Mini-Mental State Examination[27] and the Iowa Screening Battery for Mental Decline[28] were also given as part of the second examination assessment of cognitive status. They are included in the present analysis as measures of global cognitive functioning concurrent with the second assessment of Digit Symbol performance. As a measure of mental status at examination 2, scores from the Center for Epidemiologic Studies–Depression Scale[29] were also included in the present analysis.

Biologic measures for the present analysis included systolic and diastolic blood pressures and heart rates that were measured at rest. A standard clinical laboratory assay was used to determine the concentration of cholesterol, glucose, triglycerides, and thyroxine in blood. The forced expiratory volume in 1 second/forced vital capacity from the standard spirometric measurement of the forced expiratory maneuver was obtained, and measured weights and heights were used to compute the body mass index in kilograms divided by the square of height in meters. The presence of cardiovascular disease (angina pectoris, coronary insufficiency, myocardial infarction, aortic valve disease, hypertension, diabetes, and/or atherosclerotic infarction of the brain) was determined by history and physician interview.

Behavioral measures included questionnaire assessment of smoking history (amount smoked and years smoked), from which a measure of lifetime exposure (pack-years) was constructed, and use of alcohol (ounces consumed per day). Thurstone[30] Activity (ie, a measure of a characteristic activity level that is associated with a measured level of physical activity) and a measure of Type A behavior (ie, a structured interview) were also collected. The taped interview was subsequently reviewed by independent raters for the Type A behavior determination. Background variables included measures of age and years of education.

Statistical Methods

Average decline in Digit Symbol performance was calculated for all twins and for MZ and DZ twin pairs separately. Means, total variances, and within- and among-pair mean squares for Digit Symbol performance at each of the two examinations and for the change in performance across examinations were compared between the two zygosities with the corresponding t' and F' tests, as proposed by Christian et al.[31] The heritability analysis of Digit Symbol performance at each of the two examinations relied on a comparison of the Z-transformed intraclass correlations for each zygosity and the calculation of broad heritability (h^2) according to the formula $h^2 = 2(r_{MZ} - r_{DZ})$.

Because of the large observed variance in Digit Symbol change scores in this relatively small sample, we did not perform a heritability analysis on change scores. Instead, we examined pairwise twin concordance for decline in each zygosity—defined as a threshold value of change in both twins of greater than or equal to 6, or about 1 SD. We also examined discordance for decline—defined as a difference between co-twins of greater than or equal to 6 in the change in performance. This classification of change scores resulted in five MZ twin pairs and one DZ twin pair concordant for decline and 11 DZ twin pairs and six MZ twin pairs discordant for decline. Of the latter six MZ twin pairs, all of the decliner twins had scores that dropped by eight or more points, with none of the co-twins showing a decline of more than two points. Two of the six nondeclining co-twins had an improvement in performance over the two examinations. The ratio of these concordances in MZ and DZ twin pairs was used as a test for the presence of genetic effects.[32] The prevalence of decline was also compared between the two zygosities.

The next step in the analysis was to investigate similarities and differences on biologic and behavioral variables, measured at examination 1 between (1) MZ twin pairs concordant for decline in relation to all MZ twins in the sample and (2) intrapair differences within MZ co-twins discordant for decline, in relation to the mean difference in all MZ twin pairs. The mean values for the concordant twins and the mean intrapair differences for the discordant twins were compared with the corresponding 99% confidence interval (CI) around the mean for all MZ twins or the average intrapair difference over all MZ twin pairs, respectively.

All biologic, behavioral, and disease measures were taken at examination 1. Their relationship in time to the measures of subsequent change on Digit Symbol performance permits us to view them as possible predictors of decline. The mental status measures (ie, the Mini-Mental State Examination, Iowa battery, and Center for Epidemiologic Studies–Depression Scale) were collected at the second examination only and are included in this analysis to document the adequacy of global cognitive function in study participants.

These analyses were designed to identify (1) biologic and behavioral characteristics that covary with significant decline in genetically identical individuals and (2) individual environmental characteristics that also are associated with decline. Variables that differentiated MZ twin pairs who were concordant for decline in performance from the whole sample could be associated with decline through shared genetic effects, shared environmental effects, or both. Variables that showed a significant difference within the MZ twin pairs that were discordant for decline were the result of individual nonshared environmental effects only.

RESULTS

Heritability Analyses

The mean raw scores on the Digit Symbol subtest at examination 1 for MZ and DZ twins were 50.6 and 49.9, respectively. Average decline in Digit Symbol performance during the 5-year period was 3.9 (SD, 5.7), and it was significantly different from 0 ($P<.0001$). For MZ twins, the mean decline was 4.4 (SD, 6.6), and for DZ twins, the mean decline was 3.6 (SD, 4.7). No significant difference in the mean decline by zygosity was observed. The mean scores at both test times were consistent with expectations for age (equivalent to an age-scaled score of 10 to 11 based on Wechsler Adult Intelligence Scale–Revised norms).

Heritability analysis of Digit Symbol performance at each of the two examinations revealed consistent evidence for a genetic component. At the first examination, the intraclass correlation for MZ twin pairs was .85, while

Table 1.—Characteristics of MZ Twin Pais Concordant for Significant Decline in Digit Symbol Performance*

	MZ Pairs Concordant for Significant Decline on Digit Symbol (n=10), Mean	Overall MZ Twins (n=53)	
		Mean	99% CI
Measures at examination 1			
Age, y	58.40†	57.14	56.00, 58.28
Education, y	12.60†	13.87	12.97, 14.77
FEV_1/FVC	0.68†	0.74	0.71, 0.77
Mean SBP, mm Hg‡	135.83†	124.97	119.29, 130.65
Mean DBP, mm Hg‡	84.96†	79.43	76.10, 82.76
Pack-years	21.42	18.80	9.77, 27.83
Alcohol, oz/d	0.37	0.44	0.23, 0.65
Thyroxine, nmol/L	97†	106	100, 113
Glucose, mmol/L	8.4	9.0	8.1, 10.0
Cholesterol, mmol/L	5.14	5.27	4.96, 5.58
Triglycerides, mmol/L	1.58	1.51	1.24, 1.78
HR, bpm	63.80	63.51	59.74, 67.28
Type A§	2.40	2.55	2.29, 2.81
BMI	26.90	26.05	25.10, 27.00
Thurstone Activity	67.60	66.36	63.32, 69.40
Mental status at examination 2			
Mini-Mental State Examination	28.90†	28.42	27.96, 28.88
Iowa battery	5.63†	4.72	4.00, 5.44
Depression	28.80	26.66	24.36, 28.96

*MZ indicates monozygotic; CI, confidence interval; FEV_1/FVC, forced expiratory volume in 1 second/forced vital capacity; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; and BMI, body mass index.

†Denotes a mean that is outside the 99% CI for all MZ twins.

‡Age-adjusted blood pressure values were also calculated and compared, with the difference between the means for MZ pairs concordant for decline and for all MZ twins remaining significant.

§The Type A rating was reverse scored so that lower scores are indicative of higher levels of Type A behavior.

that for DZ twin pairs was .35, with the difference between the Z-transformed correlations being significant ($Z=2.84$, $P=.002$). The estimate of broad heritability was .80. At the second examination, the intraclass correlation for MZ twin pairs on Digit Symbol performance was .79, and that for DZ twin pairs was .25. The difference in the Z-transformed r values was also significant ($Z=2.52$, $P=.006$). Broad heritability at examination 2 was estimated as .88. The prevalence of decline was similar for MZ and DZ twins, ie, 35% and 39%, respectively. Pairwise concordance for decline was 45% for MZ twin pairs and 8% in DZ twin pairs, with the difference being significant at $P<.01$.

Characteristics of Twins Concordant for Significant Decline

Table 1 shows the mean values of selected characteristics of the five MZ twin pairs concordant on decline in relation to the means of all MZ twins as individuals. The MZ twin pairs concordant for decline were significantly ($P<.01$) older (mean, 58.40 vs 57.14 years) and less educated (mean, 12.60 vs 13.87 years), with poorer lung function (mean forced expiratory volume in 1 second/forced vital capacity, 0.68 vs 0.74), higher systolic and diastolic blood pressures (mean systolic blood pressure/diastolic blood pressure, 135.83/84.96 vs 124.97/79.43 mm Hg), and lower thyroxine values (mean, 97 vs 106 nmol/L). A marginally higher level of obesity in twins concordant for decline, as indexed by the body mass index (mean, 26.90 vs 26.05), was also observed (95% CI, 25.32, 26.78).

The twins who declined on Digit Symbol performance did not exhibit deficits on the mental status screening measures. In fact, twins who declined on Digit Symbol performance showed slightly but significantly higher levels of memory performance on the Mini-Mental State Examination (mean, 28.90 vs 28.42) and on the Iowa battery (mean, 5.63 vs 4.72), compared with all MZ subjects. This lack of association suggests that, for normal individuals, the processes that are tapped by the Digit Symbol subtest are relatively independent of the functions that are measured by mental status examinations, which principally assess the sense of visual orientation, language, and memory, and are less dependent on speed of response. We note, however, that the twins who were concordant for decline on the Digit Symbol subtest also reported marginally higher levels of depressive symptoms (mean, 28.80 vs 26.66) than MZ twins as a whole (95% CI, 24.92, 28.40).

Characteristics of Twins Discordant for Significant Decline

Analysis of the MZ twins discordant for decline revealed that, compared with their co-twins with less decline, the decliner twins had significantly ($P<.01$) higher levels of systolic blood pressure (mean, 128.12 vs 115.95 mm Hg) and higher Type A behavior scores (mean, 2.83 vs 2.17) (reverse scored) at the time when they were

Table 2.—Characteristics of MZ Twin Pairs Discordant for Decline in Digit Symbol Performance*

	Mean Levels for Discordant Twins (n Pairs=6)			Mean Intrapair Difference Overall MZ Twin Pairs (n Pairs=23)	
	Decliners	**Nondecliners**	**Mean Difference†**	**Mean**	**99% CI**
Measures at examination 1					
Age, y	55.2	55.2	. . .	. . .	. . .
Education, y	13.00	12.83	0.17	−0.09	−1.30, 1.12
FEV_1/FVC	0.78	0.80	−0.02	−0.01	−0.06, 0.04
Mean SBP, mm Hg	128.12	115.95	12.17‡	0.72	−6.74, 8.18
Mean DBP, mm Hg	79.11	76.17	2.94	−0.75	−5.11, 3.61
Pack-years	23.42	18.67	4.75	7.49	−8.33, 23.31
Alcohol, oz/d	0.62	0.38	0.24	0.24	−0.07, 0.55
Thyroxine, nmol/L	118	111	7	2.45	−8.24, 13.13
Glucose, mmol/L	11.7	9.5	2.2	0.7	−1.0, 2.5
Cholesterol, mmol/L	5.20	5.36	−0.16‡	0.43	0.06, 0.80
Triglycerides, mmol/L	1.44	1.63	−0.19	0.08	−0.23, 0.39
HR, bpm	62.17	67.00	−4.83‡	4.78	−1.52, 11.08
Type A	2.17	2.83	−0.67‡	0.13	−0.33, 0.59
BMI	26.74	26.57	0.17	0.33	−0.55, 1.21
Thurstone Activity	71.67	67.00	4.67	1.13	−3.69, 5.95
Mental status at examination 2					
Mini-Mental State Examination	28.33	28.33	00.00	0.09	−0.76, 0.94
Iowa battery	4.37	4.85	−0.48	−0.05	−1.21, 1.11
Depression	27.00	24.67	2.33	0.65	−4.17, 5.47

*For explanation of abbreviations, see asterisk footnote to Table 1.

†Intrapair difference for twins discordant for decline on Digit Symbol was computed by subtracting values for twins with less decline from values for twins with more decline. Positive values indicate that twins with more decline scored higher than their co-twins.

‡Denotes a mean difference outside the 99% CI for all MZ twin pairs.

first assessed (Table 2). Twins with greater decline also showed significantly lower levels of serum cholesterol (mean, 5.20 vs 5.36 mmol/L) and heart rate (mean, 62.17 vs 67.00 beats per minute) than their co-twins with less decline. Also observed were marginally significant trends for decliner co-twins to have higher diastolic blood pressures (mean, 79.11 vs 76.17 mm Hg; 95% CI difference, −4.06, 2.56) and higher blood glucose levels (mean, 11.7 vs 9.5 mmol/L; 95% CI difference, −0.60, 2.1) and lower levels of triglycerides (mean, 1.44 vs 1.63 mmol/L; 95% CI difference, −0.16, 0.31). Twins discordant for decline did not differ to any greater degree than all MZ twin pairs on depression ratings or mental status scores.

COMMENT

In this analysis, we have documented the occurrence of a significant decline in Digit Symbol performance during a 5-year interval, and we have also demonstrated that performance on the Digit Symbol subtest is heritable at each of the two examinations at a level that is consistent with our findings in a larger sample of these twins.[6] The stability of the genetic component in older twins that was observed here has not been reported previously, to our knowledge. Evidence that indicated the presence of a significant genetic component to *decline* in performance levels during the 5-year examination interval was also obtained. This suggests that a portion of the rate of aging, as indexed by changes in psychomotor speed, may be influenced by genetic factors.

A further analysis of the variables that distinguished MZ twin pairs concordant for decline from MZ twins as a group revealed several predictors of decline. These included expected variables, such as age and education, with the declining twins being older and less educated. However, declining twins also had significantly lower levels of lung function—a sensitive physiologic measure of aging.[33] Lower thyroxine levels at the first examination were also noted and could be associated with age-related decreases in metabolic rate or thyroid hormone secretion secondary to changes in body composition also known to occur with age.[34] It should also be noted that lower levels of thyroid function, as seen in hypothyroidism, are associated with sluggish mental function.

The findings for blood pressure in twins concordant for decline are consistent with those from previous research that showed a relationship between elevation in blood pressure and decrements in cognitive performance.[35,36] Examination of disease status revealed that three of the 10 twins were hypertensive and/or receiving medication for hypertension; this prevalence was somewhat higher than that for all MZ twins (15%). To evaluate the contribution of hypertensive disease per se to this relationship, we examined the mean systolic and diastolic blood pressures for the twins concordant for decline, after eliminating the three twins with diagnosed hypertension. The resulting means for systolic and diastolic blood pressures, ie, 129.6 and 82.8 mm Hg, respectively, remained outside the upper boundaries for the corresponding 95% CIs, ie, 120.66, 129.28, and 76.90, 81.96, respectively. This result suggests that a causal association between elevated blood pressure and performance decrements is not dependent on the clinical expression of hypertensive disease.

The individual variables that were significant within MZ co-twins discordant for decline in performance are particularly interesting because of their independence of shared genetic and age effects. Relative to their nondeclining co-twins, decliners scored higher on Type A behavior characteristics, and they had higher systolic blood pressures. These variables are known to increase with age.[18,37]

The decline in cholesterol levels in older males has also been noted previously and, although not well understood, may be related to changes in metabolic factors.[38] The fact that previous research has identified this decline in male samples that were generally older (ie, ≥70 years) suggests that in this subset of subjects, a process, perhaps metabolic in origin, could be initiated early, leading to decrements in performance before the appearance of clinically relevant disease.

As we did for concordant MZ decliners, we reexamined blood pressure differences in the discordant decliners by excluding the twin pair in which one co-twin had hypertensive disease. The mean intrapair difference diminished for systolic blood pressure (8.4 mm Hg) but remained significantly larger ($P<.01$) than the average intrapair difference in all twin pairs. Although the mean intrapair difference for diastolic blood pressure also declined and, subsequently, became not significantly different from that of all twin pairs, it should be pointed out that in four of the five twin pairs in this analysis, the declining twins had substantially higher levels of both systolic and diastolic blood pressures than did their nondeclining co-twins. Thus, this analysis, as did the one for concordant twins, suggests that elevated blood pressure may be associated with a decline in performance that is *independent* of the diagnosis of clinical disease.

The twins in this sample represent a generally healthy subset of the aging population. Their levels of biologic, behavioral, and psychologic characteristics are consistent with published values for populations of similar age.[39] Yet, within the broad category of "normal aging," there is often marked interindividual variability on biologic and psychologic measures. This study suggests that genetic and shared environmental factors play a role in normal aging decline, and that when these sources of variance are controlled, individual differences in blood pressure and other factors may contribute to heterogeneity in cognitive performance.

Because many different cognitive skills are engaged during Digit Symbol performance, differences in scores cannot be attributed to a single brain mechanism or substrate. However, according to Salthouse[40] and others, Digit Symbol performance may index a basic process of central nervous system slowing. Such slowing is one of the most predictable correlates of aging[41] and has important implications for a wide range of skilled performances. In this study, decline in Digit Symbol scores was not associated with poor performance on mental status screening examinations. However, if more sensitive measures had been included in the test battery, additional declines in cognitive function might have been observed.

An obvious limitation of the present analysis is the relatively small sample size. This precluded the use of multivariate procedures to control for covariation among the examined characteristics in relation to the differences between decliners and nondecliners. We believe, however, that continued follow-up of the twins is justified by these results. We expect that as the twins in this cohort age, differences in decline will become greater[42] across a wider variety of measures, including memory assessment. It will be possible to observe whether the decline in memory follows the same trajectory as does the decline in psychomotor speed and the extent to which this decline in memory is affected by the same or different risk factors.

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Intranasal Apomorphine in Parkinsonian On-Off Fluctuations

Teus van Laar, MD; Ernst N. H. Jansen, MD; A. W. Guus Essink, PharmD; Cees Neef, PhD

• The efficacy of intranasal apomorphine was assessed in seven patients with Parkinson's disease and severe levodopa (L-dopa)–related "off-period" disabilities. All patients responded favorably to treatment with intranasal apomorphine. The speed and the quality of motor response and the pharmacokinetic profile showed results similar to those seen after subcutaneous injection of apomorphine administered by insulin pen syringe. The simplicity in the technique of intranasal apomorphine administration was found to be superior by all patients.

(*Arch Neurol.* 1992;49:482-484)

The frequency of treatment "on-off" fluctuations in patients with idiopathic Parkinson's disease increases with the duration of levodopa (L-dopa) treatment. The off periods are usually refractory to existing treatment regimens like dose fractionation of levodopa, sustained-release levodopa preparations, and comedication with dopamine agonists. In 1976, Cotzias et al[1] already reported the clinical benefit of oral apomorphine in the treatment of patients with Parkinson's disease. Unfortunately, oral apomorphine caused azothemia, which was the reason to stop this route of administration. Recently,[2] subcutaneous apomorphine was shown to have a predictable, consistent, rapid, and safe efficacy for otherwise refractory disabling off periods. This direct-acting, very potent dopamine agonist with a high affinity for both D_1 and D_2 receptor subtypes was proved to be an important tool in the treatment of on-off fluctuations. Since then, the efficacy of subcutaneous apomorphine in the management of off-period problems and response fluctuations has been documented.[3-6] Long-term follow-up has shown no tachyphylaxis.[7] A preliminary study[8] has indicated that rectal apomorphine offers an effective adjunct to subcutaneous injection in selected patients. Subcutaneous apomorphine application has a few disadvantages.[9] Continuous application by a pump device, as well as intermittent injections by penlike injection system with apomorphine, can give rise to subcutaneous red nodules, as a result of an inflammatory reaction of the subcutaneous tissue to apomorphine or the subcutaneous needle. Another disadvantage sometimes is the problem to cope with the penlike injection technique or pump device in an off period. Kapoor et al[10] recently described their preliminary results with the easy-to-handle method of intranasal application of apomorphine. In an open experimental study design, we assessed clinical and pharmacokinetic parameters of the efficacy of intranasal apomorphine in off periods.

We describe the results of intranasally administered apomorphine in seven patients.

PATIENTS AND METHODS

Seven patients with idiopathic Parkinson's disease were included in this study. All patients agreed to participate in the study, and they gave informed consent after full disclosure of potential risks and benefits. The patients were free of instable renal, hepatic, hematologic, cardiovascular, pulmonary, or other significant diseases that could interfere with compliance or drug action. Patients were admitted to a hospital during the study period. They had a mean age of 58.2 years (range, 29 to 71 years) and a mean duration of levodopa treatment of 9.3 years (range, 2 to 20 years). Response fluctuations had been present in these patients for more than 6 months. Levodopa and dopamine agonist medication regimens were kept unchanged 1 month before entry into the study. Sustained-release levodopa preparations had been of marginal benefit in the past to all these patients. All patients were known to respond favorably to treatment with subcutaneous apomorphine in their off periods.

Before starting this study, the ciliotoxicity of apomorphine had been assessed by applying it to the nasal mucosa of chickens.[11] No ciliotoxicity of apomorphine could be established.

Before entry into the study, each patient was examined by our ear, nose, and throat specialist. Patients with an allergic or otherwise pathologic nasal mucosa were excluded. The nasal mucosa of each patient was examined again at the end of the study.

The intranasally applied apomorphine consisted of a 1% solution (10 mg/mL) of apomorphine, with the use of a metered dose nebulizer that delivered 0.1±0.05 mg (mean±SD) of solution with each application by puff (produced by Blocklandpak BV, Hoogblokland, the Netherlands).

Patients were titrated on an optimal dose of apomorphine, in separate periods, starting with a single puff (corresponding with 1 mg of apomorphine) in one nostril, until an optimal clinical response (ie, the maximum tolerated dosage resulting in the most beneficial motor response) was seen. The time between each application was at least 2 hours, irrespective of any other off period in the interval, so as to prevent bioactivity of a preceding apomorphine application.

All patients were given the peripheral dopamine receptor antagonist domperidone, 20 mg three times daily, as oral premedication at least 24 hours before they were studied.

Before and after each application of intranasal apomorphine, a qualitative neurologic rating with the Columbia Scale was done, as well as a quantitative rating, consisting of finger tapping and foot tapping,[12] timed walking over a 25-meter course, and a pinboard test. Clinical ratings were performed twice at each apomorphine experiment: (1) at time 0 in the off period directly before application and (2) at the time of maximal motor response. The duration and the magnitude of response were estimated. Blood pressure was measured before and also a quarter of an hour after application of intranasal apomorphine. The serum apomorphine levels were drawn at times 0, 3, 6, 9, 12, 15, 20, 30,

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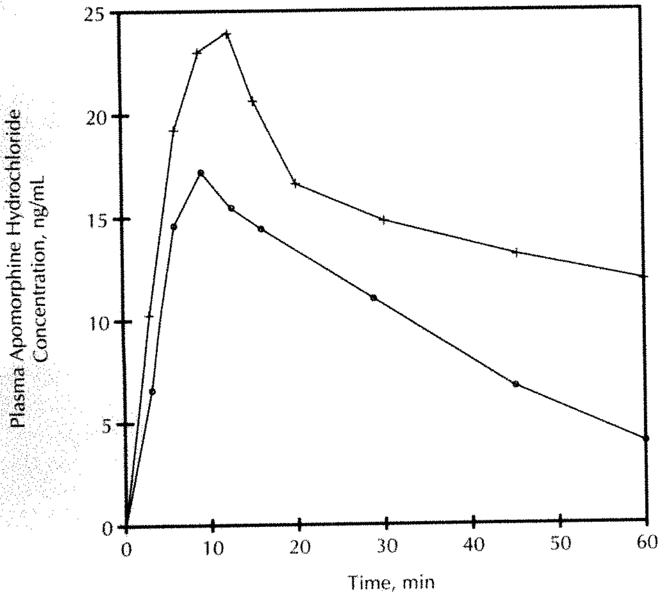

Fig 1.—*Plasma concentrations of apomorphine hydrochloride in one patient. The upper curve indicates after 5 mg of subcutaneous apomorphine given; the lower curve, after 4 mg of intranasal apomorphine given.*

and 60 minutes and analyzed with a high-pressure liquid chromatography method.[13]

The results of qualitative and quantitative data of motor responses before and after application of intranasal apomorphine were analyzed statistically with the use of the Wilcoxon Signed-Rank test. The ratings of the four items of the quantitative motor scales were summed to give an estimation of the total quantitative score.

RESULTS

All patients, who were included, showed an evident positive clinical response with intranasally administered apomorphine.

The doses of apomorphine hydrochloride that were needed for an optimal response in four patients ranged from only 1 to 2 mg (one to two puffs). Two patients needed 4 to 5 mg, and one patient needed 10 mg.

There was no correlation between the dose of intranasal apomorphine and latency of onset. The mean latency of onset varied from 5 to 15 minutes (mean, 8.8 minutes). A similar latency of onset was reported previously by the same patients with the use of subcutaneous apomorphine, with comparable clinical improvement (Fig 1).

The duration of response in the whole group varied from 26 to 90 minutes (mean, 49 minutes). The four patients who needed 1 to 2 mg had a duration of response that varied from 25 to 45 minutes. In the two patients who needed 4 to 5 mg, the duration of response was 60 minutes. The patient with 10 puffs (10 mg) had a duration of response that varied from 60 to 75 minutes. The duration of effect thus seemed to be dose dependent, although there was a substantial interindividual variation.

All Columbia motor disability rating scale variables improved significantly with apomorphine, especially bradykinesia ($P<.001$). Also, gait and rigidity improved significantly ($P=.006$). The improvement of postural stability showed a lesser significance ($P=.02$) (Fig 2).

The quantitative parameters of motor response showed a significant improvement of all items that were measured. Foot tapping and finger tapping especially improved ($P=.002$ and $P=.001$, respectively), but pinboard testing also had a significant positive efficacy ($P=.005$). Walking assessments showed a lesser improvement ($P=.04$) with intranasally administered apomorphine.

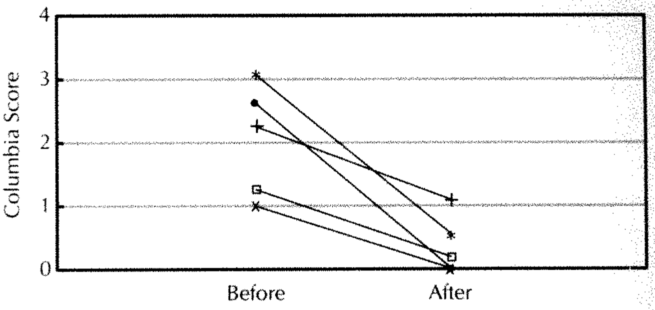

Fig 2.—*Scores of separate Columbia items before and after intranasal apomorphine hydrochloride treatment (mean of seven patients). Wilcoxon Signed-Rank test was used. Closed squares indicate tremor (P=.004); open squares, stability (P=.02); plus signs, rigidity (P=.006); times signs, gait (P=.006); and asterisks, bradykinesia (P<.001).*

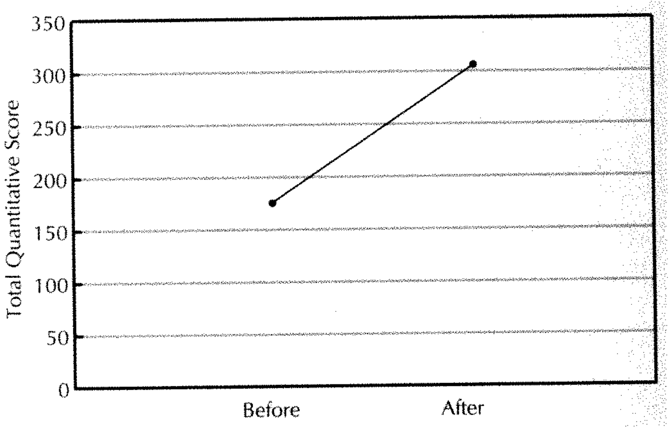

Fig 3.—*Total quantitative score of seven patients before and after intranasal apomorphine hydrochloride treatment. Wilcoxon Signed-Rank test, P=.001.*

When the total Columbia motor disability ratings of all patients were observed, the mean value of all ratings showed a significant improvement ($P=.0005$); the same held true for the quantitative scores ($P=.001$) (Fig 3).

In the whole group, there was a variance from 4 to 9 minutes of the time of maximal concentration (Tmax) (mean, 7 minutes). The maximal concentration (Cmax) varied from 12 to 85 ng/mL (mean, 25 ng/mL) (Fig 4). Although these pharmacokinetic data do show a definite positive correlation between the dosage and plasma level, the magnitude of the motor response did not seem to be critically dependent on the dosage of apomorphine that was administered.

No patients showed adverse effects, such as nausea, hypotension, or psychosis. In all patients, domperidone medication could be stopped without problems of adverse events after 2 weeks. Four patients yawned, just before clinical benefit was experienced. One patient had paresthesias in his legs at the moment of improvement of his rigidity. Five patients showed moderate dyskinesias after optimal-dose titration; these dyskinesias were of the same severity as those that were seen after subcutaneous apomorphine injection.

Only one patient (the one with the 10-mg dose in each

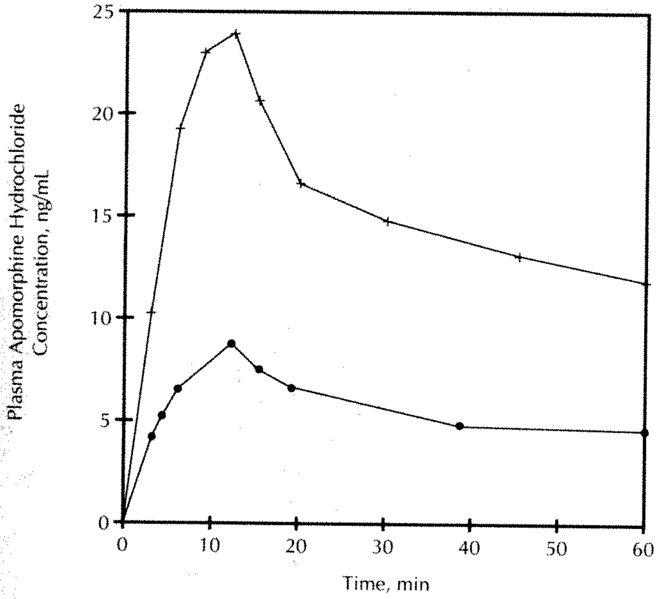

Fig 4.—*Plasma concentrations of apomorphine hydrochloride in one patient. The upper curve indicates after 4 mg of intranasal apomorphine given; the lower curve, after 1 mg of intranasal apomorphine given.*

off period) very soon experienced a severe nasal vestibulitis within 4 weeks after intranasal apomorphine application. Intranasal apomorphine application was discontinued in this patient afterward.

After some weeks, three patients showed a slight form of vestibulitis that consisted of nasal blockage and black crustae in the vestibulum nasi, not interfering with the efficacy or compliance of intranasal apomorphine applications. It was not necessary to treat this slight form of vestibulitis by topical application of xylometazoline chloride. All three patients elected to continue intranasal apomorphine applications. These three patients with vestibular crusting or nasal blockage, and also the other three patients without nasal adverse events, now have received intranasal apomorphine for 9 months, without other side effects and without progression of the nasal vestibular signs or symptoms. In all six patients, long-term intranasal apomorphine administration continued to be effective and safe for relieving off-period disabilities. Regular otorhinolaryngologic assessment was established in all patients.

CONCLUSIONS

The results of this study confirm the suggestion of Kapoor et al[10] that the intranasal application of apomorphine might offer an effective alternative to subcutaneous injection of apomorphine.

All patients in this study switched fully "on" with intranasal apomorphine after dose titration had been accomplished. The qualitative and quantitative parameters of their motor responses reached a clear statistical significance.

The doses of intranasal apomorphine, necessary to shoe a good response, were similar to that seen after subcutaneous use.

Also, the magnitude of the motor response after intranasal apomorphine application was equal as compared with subcutaneous apomorphine injections. The duration of response only was slightly shorter with intranasal apomorphine applications. In our experience, the duration of response correlated positively with the dosage that was used. The latency of onset of response, however, was comparable with both routes of administration.

Therefore, the use of intranasal apomorphine is a very easy and effective procedure to realize a rapid and consistent, predictable relief of off-phase problems. Figure 1 shows a very high area under the curve (bioavailability) of intranasal apomorphine as compared with that of subcutaneous apomorphine (90% to 100%). This nasal absorption is also much better as compared with that in a recent report about sublingual apomorphine, with an area under the curve of 10% to 22%.[14]

A high dosage of single intranasal apomorphine applications, however, seems to make patients preponderant to vestibulitis; this lowers nasal mucosal absorption substantially. Besides vestibulitis, there are no other adverse effects. The use of intranasal morphine and cocaine caused much more difficulties, and therefore, these drugs are not comparable with intranasal apomorphine. In patients who are known to respond to subcutaneous apomorphine hydrochloride at a low dose (<4 mg), the above-mentioned results seem to be very promising for a wider and long-term use of the intranasal apomorphine spray. It seems prudent to advise regular ear, nose, and throat investigations.

Intermittent intranasal apomorphine application is a very easy-to-handle procedure, and it seems to be a useful adjunct in the management of otherwise refractory off-period problems.

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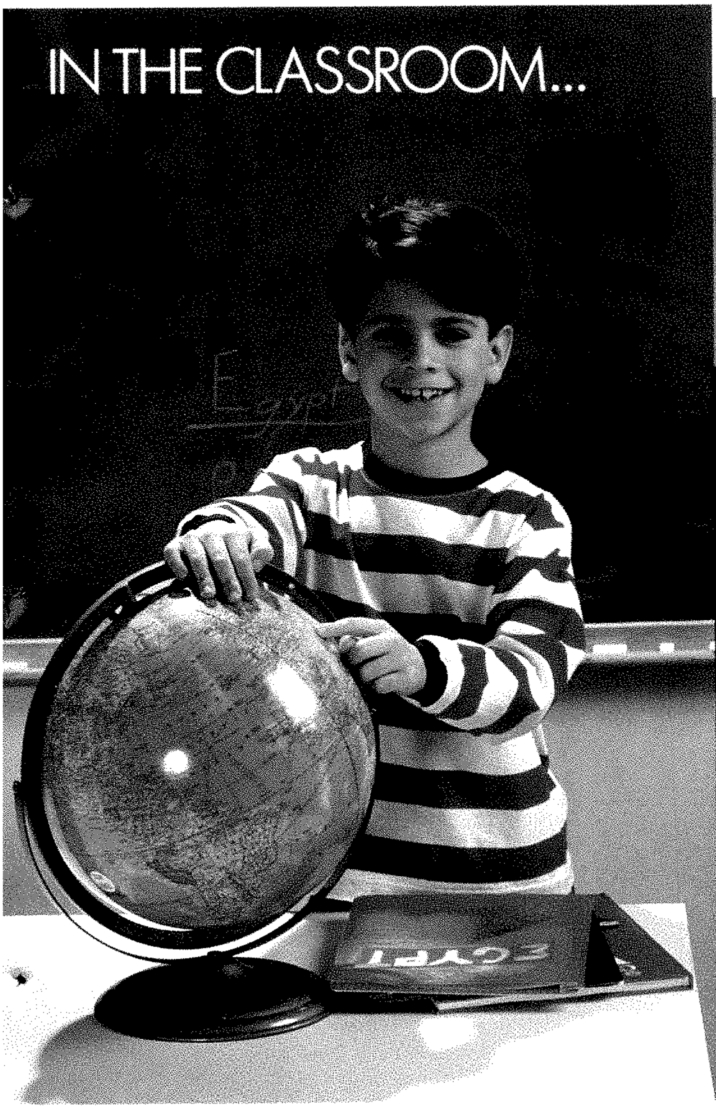
Seizures controlled, thoughts clear, smiles bright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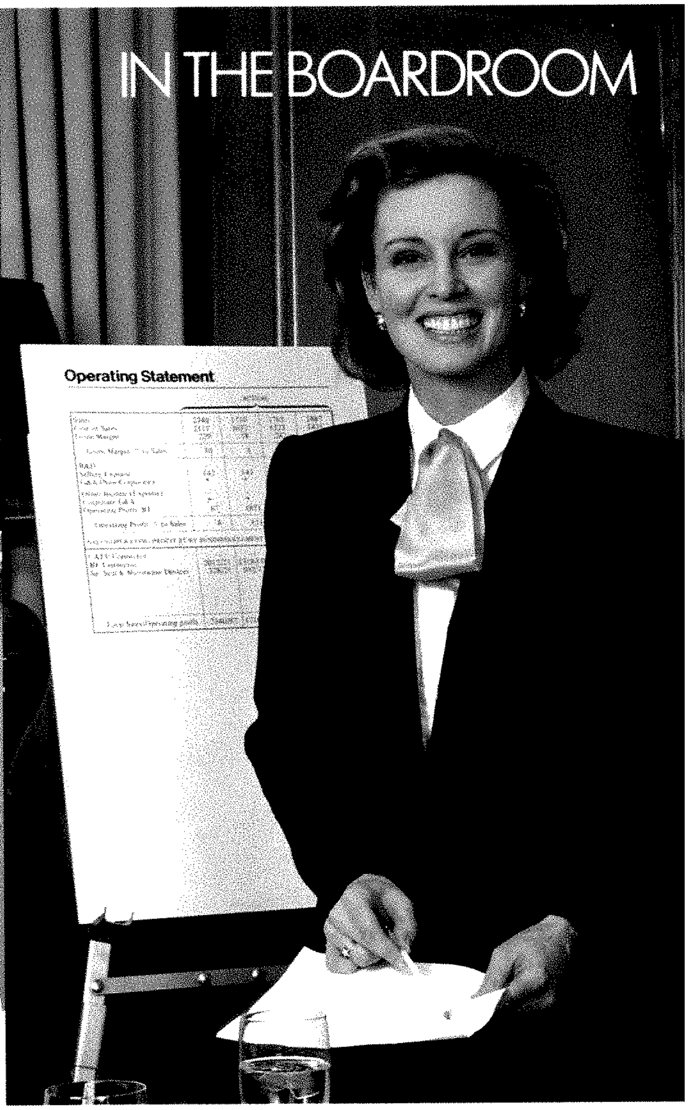

Low risk of cognitive impairment[1]

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References:

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WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

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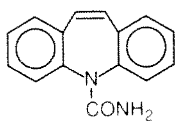
BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, and as a suspension of 100 mg/5 ml (teaspoon). Its chemical name is 5*H*-dibenz[b,f]azepine-5-carboxamide, and its structural formula is:



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Tablets: Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

In clinical studies both suspension and conventional tablet delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster than the tablet. Following a b.i.d. dosage regimen, the suspension has higher peak levels and lower trough levels than those obtained from the tablet formulation for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4 to 5 hours after administration of oral tablets. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

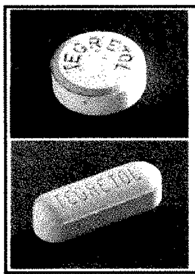
1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.



Only TEGRETOL
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10,11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid, fluoxetine or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of

6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: Either 200 mg b.i.d. for tablets or 1 teaspoon q.i.d. for suspension (400 mg per day). Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: Either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension (200 mg per day). Increase at weekly intervals by adding up to 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg/daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 58887-052-30
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 58887-052-32

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

Bottles of 100	NDC 58887-027-30
Bottles of 1000	NDC 58887-027-40
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 58887-027-32

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture. Dispense in tight container (USP).

Suspension 100 mg/5 ml (teaspoon)—yellow-orange, citrus-vanilla flavored

Bottles of 450 ml	NDC 58887-019-76

Shake well before using.

Do not store above 86°F.

Dispense in tight, light-resistant container (USP).

Printed in U.S.A. C91-50 (Rev. 11/91)

BASEL Pharmaceuticals

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Division of
CIBA-GEIGY Corporation
Summit, New Jersey 07901

Dosage Information: Tablets and Suspension

Indication	Initial Dose		Subsequent Dose		Maximum Dose
	Tablet	Suspension	Tablet	Suspension	Tablet or Suspension
Epilepsy					
6-12 years of age	100 mg b.i.d. (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 100 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 1 teaspoon (100 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours
Over 12 years of age	200 mg b.i.d. (400 mg/day)	1 teaspoon q.i.d. (400 mg/day)	Add up to 200 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 2 teaspoons (200 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours: 12-15 years 1200 mg/24 hours: over 15 years 1600 mg/24 hours: adults, in rare instances
Trigeminal Neuralgia	100 mg b.i.d. on the first day (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 200 mg per day in increments of 100 mg every 12 hours	Add up to 2 teaspoons (200 mg) per day q.i.d.	1200 mg/24 hours

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Personality Changes in Alzheimer's Disease

Anjan Chatterjee, MD; Milton E. Strauss, PhD; Kathleen A. Smyth, PhD; Peter J. Whitehouse, MD, PhD

• How personality changes in Alzheimer's disease is not well understood. Accentuations of premorbid personality, systematic shifts in personality traits, and specific personality changes affecting subtypes of patients have been postulated. To investigate which of these alternatives occurs in Alzheimer's disease, caregivers were given a comprehensive personality inventory standardized for use by informants. Caregivers observed more neurotic, less extroverted, and less conscientious behavior. To a smaller extent, patients with Alzheimer's disease were reported as becoming less agreeable and less open. The changes in reports of neuroticism, extroversion, agreeableness, and openness suggested consistent systematic shifts across all patients. Patients with depressive features were reported to have been more neurotic; those with paranoid delusions were reported as having been more hostile. Premorbid personality traits may predispose to subsequent psychiatric symptoms in Alzheimer's disease.

(*Arch Neurol.* 1992;49:486-491)

Clinical criteria used to diagnose dementia include changes in personality.[1] Yet, the prevalence and nature of these changes in Alzheimer's disease (AD) are unclear. A number of alternatives are possible. Standard references indicate that premorbid personality may be accentuated, resulting in exaggerations of personality characteristics.[1-3] It is also possible that individuals with AD become similar to each other, converging into a unified "AD personality," with a reduction in the normal variability of personality traits. It may be that individuals with AD change in stereotypic ways, while maintaining individual variability. In this case, there would be similar systematic shifts in personality traits of the entire population of patients with AD. Another possibility is that rather than affecting all patients with AD, there may be specific subsets of individuals with AD who have particular personality changes. These divergent changes would then emerge as behavioral subtypes of the disease. Finally, it may be that there is no consistency to their observed personality changes. These changes may be epiphenomena of varied neuropathologic topographies and bear no correlation to preexisting personality structure.

Rubin and coworkers[4] used open-ended questions and the Blessed Dementia Scale[5] to investigate personality changes in AD. They found passivity in about two thirds of the patients, and agitation and self-centeredness each in a third.[4,6] These results suggest that personality changes in AD diverge into overlapping subtypes. However, the use of open-ended questions in the study makes replication of their findings difficult. Petry et al[7,8] used informant ratings of AD patients' position on bipolar continua (eg, mature-childish; energetic-lifeless) that have been standardized to describe the noncognitive effects of closed head injury. They reported a common pattern of increasing passivity, coarseness, and decreased spontaneity that was unrelated to the severity of dementia. In contrast to the previously cited study, these results imply that personality changes are similar across all individuals with AD. Although the instrument used in their study is sensitive to personality changes in neurologically impaired individuals, it is not intended to be comprehensive and is not grounded in theories of normal personality structure.

The paucity of research in this area may be a reflection of inherent methodologic difficulties in assessing personality characteristics and changes in a dementing population. Most comprehensive personality inventories are self-reports, and are inappropriate for individuals characterized by little insight, impaired judgment, and cognitive deficits. Informant-based personality inventories are uncommon. Retrospective assessments of personality introduce additional biases that are difficult to control.

The purpose of our study was to investigate changes in personality traits in AD, while attempting to minimize the inherent methodologic difficulties in assessing personality in demented patients. Chart reviews, semistructured interviews, and observer rating scales not developed to assess personality were avoided. Instead, personality was assessed using a theoretically grounded, standardized instrument designed for use by informants. We clearly distinguished between dimensions of personality traits that lie on a continuum and categorical psychiatric symptoms, and sought a relationship between the two.

PATIENTS AND METHODS

Subjects

Thirty-eight patients from the Alzheimer's Research Registry at University Hospitals of Cleveland (Ohio) Alzheimer Center

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Accepted for publication November 25, 1991.

From the Alzheimer Center, Case Western Reserve University, Cleveland, Ohio. Dr Chatterjee is now with the University of Florida College of Medicine, Gainesville.

Reprints not available.

Table 1.—NEO Personality Inventory Domains and Facets

- Neuroticism: contrasts emotional stability with maladjustment
  - Anxiety: tendency to worry and be apprehensive
  - Hostility: tendency to experience anger, irritability, and hatred
  - Depression: tendency to feel hopeless, guilty, and sad
  - Self-consciousness: tendency to feel shame and embarrassment
  - Impulsiveness: inability to control cravings and urges
  - Vulnerability: tendency to be dependent
- Extroversion: measures sociability
  - Warmth: tendency for close emotional ties
  - Gregarious: preference for other people's company
  - Assertiveness: tendency to be forceful and dominant
  - Activity: tendency to be energetic and active
  - Excitement seeking: tendency to crave stimulation
  - Positive emotions: tendency to experience positive emotions
- Openness: measures openness to a variety of experiences
  - Fantasy: tendency to have a vivid imagination
  - Aesthetics: appreciation for art and beauty
  - Feelings: receptivity to inner feelings
  - Actions: willingness to try different activities
  - Ideas: intellectual curiosity and open-mindedness
  - Values: readiness to reexamine social, political, and religious values
- Agreeableness: represents a positive orientation toward others
- Conscientiousness: represents the tendency to be organized, diligent, and reliable

that met the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised,* criteria for dementia[1] and the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for the clinical diagnosis of probable AD[9] were included in this study. They had either computed tomographic or magnetic resonance imaging scans of their head, normal thyroid function tests, normal vitamin B_{12} and folate levels, and negative syphilis serologic testing. None of the patients had previously diagnosed psychiatric illnesses. They all had modified Hachinski Ischemia scores[10] of less than 4.

The patients ranged in age from 50 to 84 years (mean, 70.7) and were moderately demented on the average (mean Mini-Mental State Examination [MMSE], 15.5; range, 3 to 26).[11] They had been ill an average of 5.3 years (range, 2 to 16 years). There were 17 (44.7%) men and 21 (55.3%) women in the sample.

Procedure

The caregivers of patients were asked to complete the NEO Personality Inventory (NEO-PI) to describe the patient. The NEO-PI assesses five major domains of personality: neuroticism, extroversion, openness, conscientiousness, and agreeableness. Brief definitions of these dimensions and the subcomponents, or facets, of the first three are presented in Table 1. The NEO-PI is standardized to be used as a self or informant report of personality.[12,13] The availability of norms for informant report based on an adult population (age range, 19 to 93 years), which may differ from norms established exclusively from college-aged subjects,[14] makes the instrument useful for this population. In adults, personality is believed to be stable over decades,[15] and Costa and McRae[13] studying self and observer reports on the NEO-PI found that over a 3-year period personality descriptions of older adults (age range, 57 to 84 years) are highly reliable ($rs > .70$) for all dimensions but agreeableness. The informants in this study consisted of a spouse in 24 (63.1%) cases and a child in 12 cases (31.6%). The informant in one case was a sister-in-law and in another a long-term companion.

Each informant completed the NEO-PI twice; once to describe the patient as he/she was prior to the onset of the illness, and once to describe the patient at the present time. For the "before" condition, informants were asked to remember when the symptoms of the patient first began, and then to pick a period several years before that to describe what the patient was like. The order in which the conditions were given was counterbalanced.

Two instruments specifically designed for the evaluation of psychopathology in AD, the Behavioral Pathology in AD[16] and Cornell Scale for Depression in Dementia[17] were used to characterize psychiatric symptoms. These ratings were based on direct examination and informant interview by raters of established reliability.[18] In this study, patients with a Cornell score of 9 or more were considered to have significant depressive features. Eight patients (21.1%) met this criterion. Twelve patients (31.6%) had paranoid delusions and six (15.8%) had hallucinations according to the Behavioral Pathology in AD. There was overlap of these psychopathologic conditions in some patients. Eight patients were exclusively paranoid, four were exclusively depressed, one patient just had hallucinations, one patient was paranoid and had hallucinations, one patient was depressed and had hallucinations, and three patients had paranoid ideation, depressive features, and hallucinations.

Data Analysis

All statistical tests (paired *t* tests, correlations, repeated measures analysis of variance, and multivariate regression analysis) were conducted using SPSS/PC+.[19] Because of the multiple, nonindependent statistical tests of the factors of the NEO-PI, a Bonferroni-type adjustment was made. The significance level for a nominal $P \leq .05$ alpha was set at $P \leq .01$ (nominal alpha, .05/5 NEO-PI variables). Only differences significant at $P \leq .01$ were considered to be reliably different. To have a common metric for comparison of change across the NEO-PI scales, mean differences between premorbid and current descriptions were standardized against the pooled SDs of premorbid and current scores. These standardized difference scores are akin to *z*-scores and permit direct comparison of the magnitude of change among subscales.

RESULTS

Personality Changes

The premorbid and current description means (±SDs) for each of the NEO dimensions and facets are presented in Table 2. Preliminary analysis did not reveal any sex differences, so the data for males and females are pooled. The premorbid characterizations of these patients were well within 1 SD of established norms, except for the trait of openness where this group was somewhat low.

There were significant changes (by matched-pair *t* test) for all five dimensions ($P < .001$). As may be seen in the column reporting standardized difference scores (Table 2), the largest changes were decreases in reported conscientiousness and extroversion, along with an increase in neuroticism. The changes in agreeableness and openness, though significant, were more modest.

Three components of neuroticism showed the greatest increases. Patients were described as having become more anxious, depressed, and psychologically vulnerable. The largest changes in extroversion were decreases in assertiveness, activity, and positive emotions, followed by warmth and excitement seeking. Patients were reported as becoming markedly less conscientious, and, although statistically significant, to a smaller degree as less open and agreeable. Within the domain of openness, patients were seen as having less openness to ideas and appreciation for art and beauty, however, they were believed to have an increasingly vivid imagination.

Table 2.—Informant NEO-PI Ratings of Patients With Alzheimer's Disease*

	Premorbid T Score	Current T Score	Standardized Change Score†
Neuroticism	51.46(±12.06)	66.79(±12.06)	1.27
Anxiety	50.53(±11.77)	63.63(±12.69)	1.07
Hostility	51.97(±12.42)	58.74(±14.40)	.51
Depression	49.42(±12.55)	66.04(±11.65)	1.24
Self-consciousness	53.73(±11.87)	60.04(±11.65)	.54
Impulsiveness	48.93(±10.74)	50.32(±08.47)	.15 (NS)
Vulnerability	53.25(±12.63)	78.39(±13.92)	1.89
Extroversion	46.30(±09.35)	34.52(±09.49)	−1.25
Warmth	49.45(±11.42)	40.21(±12.13)	−.78
Gregariousness	48.50(±11.05)	45.13(±12.51)	−.29 (NS)
Assertiveness	45.60(±10.60)	36.90(±06.45)	−1.05
Activity	47.15(±08.53)	38.71(±08.48)	−.99
Excitement seeking	47.87(±08.90)	42.17(±09.34)	−.63
Positive emotions	47.33(±10.40)	37.64(±11.48)	−.89
Openness	38.09(±09.48)	34.33(±08.61)	−.42
Fantasy	46.61(±09.49)	51.95(±10.59)	.53
Aesthetics	42.24(±12.99)	36.52(±10.86)	−.48
Feelings	42.91(±09.43)	40.44(±11.96)	−.23 (NS)
Actions	42.67(±08.73)	42.50(±09.31)	−.02 (NS)
Ideas	37.75(±09.32)	29.11(±07.94)	−1.00
Values	43.59(±09.32)	42.46(±07.89)	−.13 (NS)
Agreeableness	49.47(±12.39)	44.71(±12.56)	−.38
Conscientiousness	49.65(±08.27)	30.26(±11.85)	−1.93

$$\text{Standardized Change Score} = \frac{\text{Mean Difference}}{(\text{Premorbid SD} + \text{Current SD})/2}$$

*NS indicates not significant.
†$P\leq.001$.

There were substantially significant ($P<.001$) correlations between premorbid and current descriptions for neuroticism ($r=.76$), extroversion ($r=.67$), openness ($r=.77$), and agreeableness ($r=.79$). These correlations indicate that the positions of patients within groups remained relatively consistent although the absolute levels of the dimensions changed. The magnitude of change was similar across the entire sample. The absence of a significant correlation for conscientiousness ($r=.04$) indicates that while levels of conscientiousness decreased, the degree of change was highly variable.

To assess whether the magnitude of observed changes in personality were related to duration of illness, or mental status changes, current scores were regressed on premorbid scores. The standardized residuals, which indicate the amount of change independent of initial score on the trait, were then correlated with years of illness and MMSE scores. The correlations between neuroticism, extroversion, openness, conscientiousness, and duration of illness were not significant ($rs=-.16$ to $.10$). However, the longer a patient had the illness, the greater the perceived decrease in agreeableness ($r=-.41$, $P=.005$). Correlations between changes in neuroticism, openness, conscientiousness, agreeableness, and MMSE scores were not significant ($rs=-.01$ to $.25$). Patients with higher MMSE scores were believed to have greater reductions in extroversion ($r=-.46$, $P=.002$). This finding is difficult to explain, and begs replication.

Premorbid scores were correlated with duration of illness and MMSE to examine whether informants' memories of the patients with AD were influenced by length of time that the patient had been ill or to the degree of cognitive impairment. There was a trend for caregivers to perceive patients as having been more extroverted premorbidly the longer the patients had the illness ($r=.26$, $P<.06$). Within the domain of extroversion, patients who had been ill longer were remembered as being more excitement seeking ($r=.42$, $P<.005$). There was a trend for patients to be recalled as more gregarious ($r=-.28$, $P<.05$) and more open ($r=-.32$, $P<.05$), the greater the cognitive impairment as measured by lower MMSE scores. Within the domain of openness, the more demented patients were perceived as being more aesthetic ($r=-.47$, $P=.001$) and more receptive to inner feelings ($r=.39$, $P<.01$).

Psychiatric Symptoms

The relationship between current psychiatric symptoms and premorbid personality was examined using regression analysis. The psychiatric symptoms of depression, hallucinations, and delusions were dummy coded as present/absent and regressed on the reported premorbid NEO scores.[20] Patients with depressive features were remembered as having been more neurotic (partial, $r=.44$, $P<.01$), especially on the anxiety (partial, $r=.43$, $P<.005$), depression (partial, $r=.42$, $P<.01$), and self-conscious (partial, $r=.53$, $P<.001$) facets of this dimension. There were tendencies for patients with depressive features to be remembered as being more vulnerable (partial, $r=.37$, $P=.05$) and less extroverted (partial, $r=-.29$, $P<.08$). The only facet of extroversion that correlated with current depression was being less assertive premorbidly (partial, $r=-.38$, $P=.02$).

Patients with paranoid delusions were reported as having been more hostile (partial, $r=.42$, $P<.01$), with trends toward being remembered as less agreeable (partial, $r=-.34$, $P=.05$) and exhibiting fewer positive emotions (partial, $r=-.34$, $P=.04$). There were trends in patients with hallucinations toward being recalled as having been more open (partial, $r=.31$, $P=.06$), principally in the facets of fantasy (partial, $r=.32$, $P=.06$) and aesthetics (partial, $r=.34$, $P=.04$).

COMMENT

Methodology

The assessment of personality in demented patients is methodologically challenging. The standardization and validation of the NEO-PI as an observer report permits assessment of theoretically based, robust dimensions of personality in this population. Adult personality after the age of 25 to 30 years is believed to be relatively stable.[15,21] However, retrospective assessments risk introducing biases intrinsic to relying on memories of what a person was previously like. Although this study lacks an elderly controlled sample, our AD population's premorbid personality profile means were similar to those of the normative population (not assessed retrospectively) in the dimensions of neuroticism, extroversion, agreeableness, and conscientiousness (T scores, 46.30 to 51.40) suggesting retrospective assessments did not introduce a severe systematic bias. The fact that the patients were remembered as being less open than the norms could mean that such individuals are predisposed to developing AD, or the nature of the illness introduces a bias in recollecting the individual as having been more closed. Alternatively, volunteers for psychological research in the normative sample may have been more "open" than the population at large.

The reliability and validity of informants' memories of demented patients is not well established. Petry et al[8] recently reported stability in informants' recollections of patients with AD over a period of 3 years. In a study currently being completed, we have found substantial reliability for retrospective reports obtained nearly 1 year later (*r*s range, .63 to .92) (M. E. Strauss, PhD, M. Pasupathi, unpublished data, 1991).[21] Petry et al[7] also found that patients with AD, compared with control subjects, were remembered as being more easy-going, happy, and social prior to the onset of illness. Consistent with their findings, we found that the longer patients had AD, there was a trend to being remembered as more premorbidly extroverted, and for patients with a greater cognitive impairment, there was a trend to being reported as having been more open, as well as being more gregarious. These observations suggest that caregivers may idealize their memories of patients with AD.

Cummings et al[22] have recently reported differences in informants' reports of personality changes in demented patients of different causes. Further investigations of personality changes in different dementing populations will sort differences in overall profiles of change and will be able to assess which trait changes are common to dementia, and which are specific for AD.

Personality Change

Caregivers experienced patients with AD as having consistent and pervasive changes in the personality traits of neuroticism, extroversion, openness, and agreeableness. These results, in accord with the findings of Petry and coworkers,[7] suggest that there are stereotypic personality trait changes in AD. These trait changes occur irrespective of the individual's premorbid personality. There was no reduction in the variability of personality traits in the current assessments, suggesting that individuals with the disease do not converge into a unified "AD personality," at least not prior to more severe stages of dementia. Nor were there exaggerations of previous personality traits, such that highly neurotic individuals became more so, and less neurotic individuals remained unaffected. Instead, all patients were seen as having similar increases in neuroticism, irrespective of how neurotic they were to begin with.

Caregivers reported that patients with AD became more neurotic, specifically, more vulnerable, depressed, and anxious. They were observed to be less extroverted, particularly less assertive. All the patients were believed to become less conscientious and, to a lesser extent, less agreeable and open. Within the domain of openness, caregivers perceived patients as becoming less intellectually curious and aesthetic, but developing more vivid imaginations. Although patients with AD were perceived as becoming less conscientious, unlike the other traits, the degree of change was more variable.

The perceived increase in AD patients' neuroticism and decreases in extroversion, openness, and conscientiousness were independent of duration of illness, suggesting that these changes occur early in the illness. The reported changes in agreeableness did correlate with duration of illness, implying that patients were experienced as becoming less agreeable over time, irrespective of how agreeable or disagreeable they were initially believed to be.

Psychiatric Symptoms

Affective symptoms are common in AD.[23-30] These symptoms often occur early in the illness, with depressed mood or dysphoria being more common than major depression.[29] In this study, individuals categorized as being depressed had symptoms indicative of depressed mood rather than major depression. These individuals were remembered as premorbidly being more neurotic, or less emotionally stable.

Delusions are also common in AD.[27-33] In general, they tend to be persecutory, and are fleeting and not elaborate.[29] In this study, patients with paranoid delusions were reported as having been more hostile premorbidly. There was also a possible relationship between hallucinations and premorbid personality. There was a trend for the patient being remembered as having a more vivid imagination and being more open.

The results of this study suggest that certain premorbid personality traits may be associated with subsequent psychopathology. A combination of psychological and medical approaches to personality may help explain these findings. In general, psychology takes a "dimensional" view of personality. Behavior of an individual is believed to lie on a continuum for a given trait. In contrast, the medical model has tended to use a "categorical" approach, defining pathologic behaviors and syndromes that are discontinuous from those of normal subjects. In attempting to bridge these approaches, Claridge[34] suggests that although personality traits lie on a continuum, individuals located at extremes are more susceptible to expressing psychopathologic behavior. In these individuals signs and symptoms that are discontinuous from normal behavior are more likely to emerge. The observations in this study may be consistent with such a model relating personality traits and psychopathology. Since the entire population of patients with AD becomes more neurotic, there is a higher incidence of depressive symptoms in this population. Within the AD population patients that are premorbidly more neurotic are pushed to further extremes and may be even more likely to develop depressive features than those with lower premorbid neuroticism scores.

An alternative interpretation of these data would be that the memories of caregivers are colored by the patients psychiatric state when filling out questionnaires, such that the caregiver of a depressed individual might selectively remember more neurotic tendencies of the patient. Longitudinal studies assessing the reliability of retrospective accounts by single and multiple informants will help sort these possibilities.

Biological Correlates

In AD, senile plaques and neurofibrillary tangles are typically found in the medial temporal, inferior parietal, and frontal lobes.[35] Dramatic changes in personality occur with structural lesions of specific locations in the central nervous system. Bilateral temporal lobe lesions can cause the Kluver-Bucy syndrome, manifested by placidity, hypersexuality, and hyperorality.[36] Rage reactions have been reported in patients with inferomedial temporal lobe lesions.[37] Lesions of the nondominant parietal lobes may affect insight and disrupt emotional processing.[38-40] Dorsolateral lesions of the frontal lobe are associated with apathy, and orbitofrontal lesions are associated with disinhibition.[41] The gradual build-up of neuropathology in the temporal, parietal, and frontal areas would be expected to cause insidious and subtle changes in personality, particularly changes in emotional processing and activity levels.

The idea that even in nonpathologic states, variability in personality has a biological basis, dates back to Pavlov's ideas of nervous types,[42] and have been most elaborated in the West by Eysenck.[43] These theories contend that variability in personality traits are mediated by differences in the functional organization of the central nervous system. The exact nature of how different personality types are biologically mediated is not known. It is likely that neurotransmitter and neuromodulator systems are involved. Cloninger[44] has taken the extreme view that orthogonal personality traits are each influenced by specific neurotransmitter systems. He postulates that novelty seeking, harm avoidance, and reward dependence are mediated by dopamine, serotonin, and norepinephrine, respectively.[44] The existence of a one-to-one correspondence between personality traits and neurotransmitter systems remains an open empirical question. However, it is likely that personality traits are neurochemically influenced. Alzheimer's disease affects multiple neurotransmitter systems including acetylcholine, norepinephrine, and serotonin.[45] If neurotransmitters influence personality, one would again expect systematic shifts of personality traits in AD as is reported.

In summary, informants in this study reported consistent patterns of change in personality traits of patients with AD. These results also suggest a correlation between premorbid personality characteristics and subsequent psychiatric symptoms. As the AD population shifts away from the norm, individuals that were premorbidly further away, would be more susceptible to developing categorical psychiatric symptoms, such as depressive symptoms or paranoid delusions. Longitudinal studies will provide the opportunity to do detailed brain-behavior correlations specifically assessing the distribution of cortical pathology and investigating derangements of particular neurotransmitter systems. Such investigations may provide unique insights into the relationship between pathologic topography, neurochemistry, and personality traits as well as mechanisms for emergent psychopathologic behavior.

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A Population-Based Investigation of Parkinson's Disease With and Without Dementia

Relationship to Age and Gender

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• Because the prevalence of idiopathic Parkinson's disease (PD) with or without dementia remains controversial, we initiated a population-based investigation in the Washington Heights–Inwood section of New York, NY, so that nearly complete case ascertainment could be achieved. A "registry" was developed for the study, and we advertised in periodicals and on radio and television. Subjects, or their records, were examined by experienced neurologists, and most underwent a battery of neuropsychological tests specifically designed for assessment in this community. All data were reviewed by a team of clinicians to achieve a consensus diagnosis. The crude prevalence of idiopathic PD, with and without dementia, was 99.4 per 100 000, increasing from 2.3 per 100 000 for those younger than 50 years to 1144.9 per 100 000 for those aged 80 years and older. The crude prevalence for PD with dementia alone was 41.1 per 100 000 and also increased with age from zero for those younger than 50 years to 787.1 per 100 000 for those aged 80 years and older. Prevalence ratios were comparable with those of other published population-based studies in similar settings. After standardization, men had PD with and without dementia more frequently than did women. The major difference between patients with and without dementia was a later estimated age at onset of motor manifestations. We conclude that PD is a frequent disorder in the elderly population that affects men and whites more frequently than women and nonwhites. Moreover, dementia in patients with PD is more frequent than previously recognized and is strongly related to the age at onset of motor manifestations.

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The prevalence of idiopathic Parkinson's disease (PD) has been estimated to be between 80.6[1] and 187.0[2] per 100 000 in the general population. The age-specific prevalence ratio increases dramatically with age. For example, in patients older than 65 years, the prevalence of PD is twice that for all lower age groups combined and doubles again after age 75 years.[3] At age 65 years and older, the prevalence of PD varies from 350 to 800 per 100 000. Both gender and racial differences have been reported,[4,5] but they are not consistent.[6] Some degree of variation in reports of prevalence may be due to an imprecise definition of idiopathic PD, resulting in the inclusion of patients with secondary parkinsonism.

The frequency of dementia in patients with idiopathic PD is also controversial. It is significantly more frequent in older patients,[7-13] particularly when motor manifestations begin after age 70 years.[9] Marttila and Rinne[10] and others[11,12] report the frequency of dementia in patients with PD to be 30%. However, Brown and Marsden[13] believe the frequency of dementia to be overestimated because of the lack of specific criteria for the diagnosis of dementia.

To overcome some of the methodologic issues of previous studies, we began a population-based study of PD and PD with dementia in the community of Washington Heights–Inwood in the northern part of the borough of Manhattan in New York, NY. We attempted complete case ascertainment in the region called Community District 12 (CD12), where, according to the 1980 census, 179 941 people reside, including nearly 35 000 elderly people (defined as persons older than 60 years). We used strict criteria for the diagnosis of idiopathic PD and for the diagnosis of dementia. Our objective was to estimate the population prevalence of PD with and without dementia in this geographically limited and culturally diverse area of northern Manhattan.

SUBJECTS AND METHODS

Subject Selection

To be included as a subject, all patients must have lived within the four zip codes identified as CD12 in Washington Heights–Inwood during the period of recruitment, which was from April 1, 1988, to December 31, 1990. Subjects were identified through the development of a "registry" for PD in the community for all individuals considered to have PD or a related disorder. This registry for PD included all patients seen at the Columbia Presbyterian Medical Center who resided in the community. Patients were identified from a series of sources: admission and discharge lists from the hospital, lists from various ambulatory care sites, contact with practitioners both in the hospital and in the community, and review of their charts. The *International Classification of Diseases, Ninth Revision* codes on computer-generated billing lists from various medical sources and registries of inpatients and outpatients at local medical centers were also used to identify subjects. Announcements were placed in every local newspaper for a 2½-year period around the time of the study. Both television

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From the Departments of Neurology (Drs Mayeux, Hemenegildo, Marder, Tang, Cote, and Stern and Ms Denaro) and Psychiatry (Drs Mayeux, Marder, and Stern) and The Gertrude H. Sergievsky Center (Drs Mayeux, Tang, and Stern), Columbia University, College of Physicians and Surgeons; the Memory Disorders Clinic of the New York State Psychiatric Institute (Drs Mayeux and Stern); and the Center for Alzheimer's Disease Research (Drs Mayeux, Hemenegildo, Marder, Tang, Cote, and Stern and Ms Denaro), New York, NY.

Reprint requests to The Gertrude H. Sergievsky Center, 630 W 168th St, New York, NY 10032 (Dr Mayeux).

and radio programs carried public announcements about the study during the same period. Private practitioners and the single neurologist in the community of Washington Heights–Inwood who is not affiliated with the medical center were also personally contacted. We were also given access to medical record information from the regional Health Insurance Providers in the upper part of Manhattan. A list of individuals with home health attendants was also obtained from the Health Resources Association and reviewed to identify patients with PD.

Using names and existing telephone numbers, subjects were contacted and asked to participate. Only those subjects able to give informed consent or who had a next of kin willing to grant informed consent on his or her behalf were fully examined in the course of our investigation.

Some individuals were identified through the registry but could not be examined for a number of reasons. The medical records of these individuals were reviewed by a neurologist (R.M.) to obtain appropriate clinical information. For the purpose of our investigation, we required that these patients have documented evidence in the record of having been examined during the prevalence period and that they meet the same inclusion and exclusion criteria for PD as the patients who were examined. When no information was found, the patient was contacted at the last known address or telephone number. Patients were considered "missing" when no information was available.

Inclusion Criteria

Idiopathic PD was defined as the primary form of the disease in which review of the medical history and physical signs indicated no other disease process that could be considered the cause of the disorder. Two of the following four cardinal features of PD must have been present on clinical examination or mentioned in the medical records: resting tremor, shuffling gait, bradykinesia, or muscular rigidity.

Exclusion Criteria

Patients were excluded if they had any of the following disorders: secondary or symptomatic parkinsonism (postencephalitic) or parkinsonism resulting from any of the following drugs: phenothiazines, alphamethyldopa, reserpine, or metaclopramide hydrochloride. Patients with progressive supranuclear palsy, essential tremor, Shy-Drager syndrome, presumed striatonigral degeneration, and olivopontocerebellar degeneration were also excluded, as were patients who developed memory loss or dementia before motor manifestations of PD and any patient considered to have the "extrapyramidal form" of Alzheimer's disease.[14]

Demographic Data

Information regarding current age, date of birth, location of birth, residence since birth, occupation, and duration of formal education was obtained in the initial interview or record review. For ethnic group assignment, the US Census Bureau format was used; a similar process is used by the hospital record system. Subjects were asked to which ethnic group they belonged and were given choices. We attempted to subdivide Hispanic patients into country of origin. (The questionnaire used is available from the authors upon request.)

Clinical Evaluation

Patients underwent a neurologic examination by one of three experienced neurologists (L.J.C., K.M., or R.M.). The presence and severity of motor signs and symptoms were recorded by the physician using the Unified Parkinson's Disease Rating Scale.[15] Current medications were listed in a semistructured format by a trained interviewer, as was the history of the current illness. If the patient was unable to give a history or appeared to be demented, the interview was conducted with the next of kin. Information regarding performance of activities of daily living was obtained during the same interview with part 1 of the Blessed Dementia Rating Scale[16] and the Schwab and England[17] rating scale of activities of daily living. All interviews were conducted in either Spanish or English, according to the patient's choice.

All patients underwent a complete neuropsychological assessment (also conducted in either Spanish or English, according to the patient's choice), which included the following tests: (1) orientation from the Modified Mini-Mental State Examination[18]; (2) the Selective Reminding Test[19]; (3) a multiple-choice version of the Benton Visual Retention Test (matching and recognition)[20]; (4) five selected items from the Rosen Drawing Test[21]; (5) 15 items from the Boston Naming Test[22]; (6) the Controlled Oral Word Association Test[23] and the Animal Naming[24] test; (7) selected items from the Comprehension and Repetition subtests from the Boston Diagnostic Aphasia Examination[24]; (8) the Similarities subtest from the Wechsler Adult Intelligence Scale–Revised[25]; and (9) Identities and Oddities from the Mattis Dementia Rating Scale.[26]

These neuropsychological tests were scored and compared with a series of cutoff scores developed in a pilot study of dementia in the community. The cutoff scores and their application to diagnosis have been described previously.[27] Briefly, demonstrable impairment in memory, and a similar degree of impairment in at least two other cognitive categories, including abstract thinking, constructional ability, language, and orientation, was required for a patient to meet criteria for dementia.[28] The impairment could not have resulted from delirium or an alteration in consciousness.

The evaluation of social or occupational function, also required for the diagnosis of dementia,[28] was made with use of the Activities of Daily Living measures and medical history. We separated functional impairment due to intellectual dysfunction from that due to physical impairment. At the consensus conference, all the information derived from the neurologic examination and that derived from neuropsychological assessment were reviewed by a group of physicians and neuropsychologists, some of whom were involved in the assessment of the patient. For all dementia diagnoses, a consensus among the reviewers was required.

The diagnosis of idiopathic PD and dementia in the 22 patients not examined was made from a review of the records. For the diagnosis of idiopathic PD, we used the same inclusion and exclusion criteria. However, we required the diagnosis to have been made and entered into the medical records by the attending physician. In every case, this attending physician was a neurologist. For dementia, we required written evidence in the records of a history of intellectual impairment, verified by a neurologic examination or neuropsychological tests. For both diagnoses, we required that they had not been retracted or changed in subsequent entries in the medical record.

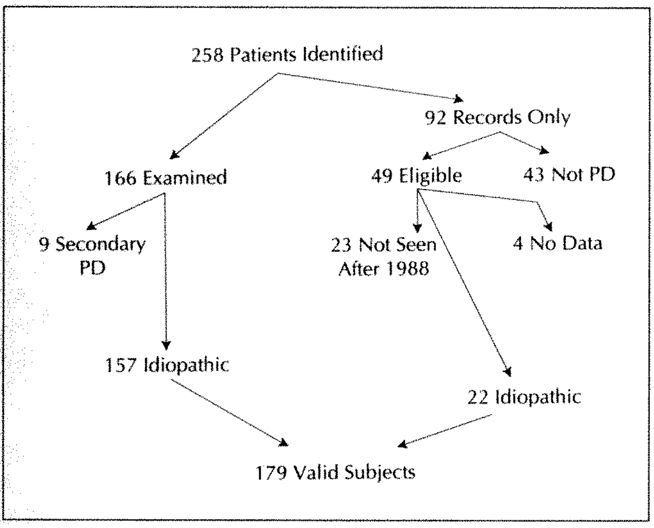
Database Management and Statistical Analysis

All data were entered by the data entry clerk and periodically checked by the project coordinators. Data were stored with the use of the Scientific Information Retrieval database management software. Analytic methods consisted primarily of calculations of rates and proportions.[29,30] To compare the prevalence of idiopathic PD between men and women and among ethnic groups, as well as to compare our data with those of other studies, indirect standardization was used.[30] We calculated standardized prevalence rates by weighting each age group based on the proportion of the age group in the total population according to the 1988 US Department of Commerce Bureau of Census estimates.[31] Each comparison between gender, ethnicity, or studies was expressed as a standardized rate ratio, defined as the ratio of the standardized prevalence rate in one group to that in another.

RESULTS

Parkinson's Disease

A total of 258 cases of presumed parkinsonism were identified by the registry, from which we determined that 179 cases (71%) were the idiopathic form of PD. The flow diagram shown in the Figure traces patient ascertainment. A total of 166 patients (64%) were examined by one of us to verify diagnosis, but only 157 were found to have idiopathic PD. The other nine patients were deemed to have secondary forms of parkinsonism. Among the 92 cases that were limited to record review, we identified 49 patients meeting inclusion criteria. The remaining 43 patients had either secondary parkinsonism (n = 15) or other disorders (n = 22); in six patients, no clinical information was available to determine diagnosis. Among the 49 eligible cases, only 22 had been examined during the prevalence period; four others were known by us to be cases, but no information was available, and 23 were not seen after April 1, 1988. Thus, the total number of valid cases for this study identified by the two methods was 179 (157 examined cases and 22 records reviewed). The remaining analyses and discussion are based only on information derived from this group of patients with idiopathic PD. Their demographic characteristics are summarized in Table 1.



Ascertainment of cases for investigation. PD indicates Parkinson's disease.

A total of 41.3% of these patients were found to have dementia during the prevalence period. Table 1 shows the demographic characteristics of the patients with and without dementia.

According to the 1980 census, 179 941 people resided in northern Manhattan. The total number of individuals in this community did not change significantly by the 1990 census, remaining within 3% of the 1980 figures. The crude prevalence of PD as of the midpoint date (July 1, 1989) was 99.48 per 100 000 persons. For the group 35 years and older, the crude prevalence was 219.8 per 100 000. The age-specific prevalence increased dramatically with age from 2.3 per 100 000 for those younger than 50 years to 1144.9 per 100 000 for those older than 80 years (Table 2). The proportion of those with dementia is presented in Table 2.

The age-specific prevalence in the community was standardized to the 1988 US census estimates.[31] There were 191.2 cases per 100 000 in the population aged 35 years and older and 86.9 cases per 100 000 for all age groups. For comparison, the standardized age-specific prevalence is shown in Table 3 for two similar studies—one in Northhampton, England,[32] and the other in Copiah County,

Table 1.—Demographic Characteristics of Patients With Parkinson's Disease in Washington Heights–Inwood*

	Patients		
Variable	Without Dementia (n = 105)	With Dementia (n = 74)	Total (N = 179)
Mean (SD) age, y	71.75 (10.1)	79.41 (7.79)†	74.92 (9.91)
% Women	51.4	51.4	51.4
Mean (SD) duration of symptoms, y	5.92 (6.22)	5.68 (5.43)	5.83 (5.92)
Mean (SD) years of education	10.05 (4.7)	9.05 (4.8)	9.63 (4.76)
% Black (not Hispanic)	4	14	8
% Hispanic	45	39	43
% White (not Hispanic)	51	47	49

*Data include all patients examined and those from record review. Washington Heights–Inwood is a community in Manhattan, NY.
†$P<.001$.

Table 2.—Prevalence of Parkinson's Disease (PD): Crude Ratios of Patients With and Without Dementia in Washington Heights–Inwood*

	Crude Prevalence†			
Age Group, y	PD Total	PD With Dementia	Proportion Demented	Population Base (1980)
<50	23 (3)	0 (0)	0	128 148
50-59	45.7 (8)	5.7 (1)	0.124	17 468
60-69	234.8 (38)	55.6 (9)	0.236	16 179
70-79	525.6 (66)	159.2 (20)	0.302	12 556
>80	1144.9 (64)	787.1 (44)	0.687	5590
All ages	99.4	41.1 (74)	0.413	179 941

*Washington Heights–Inwood is a community in Manhattan, NY.
†Values are per 100 000. Numbers in parentheses indicate numbers of patients.

Mississippi.[6] Standardized rate ratios were calculated for the comparisons between these two studies and ours (Table 3). As is apparent, the standardized age-specific prevalences differ primarily in the younger patients.

We also calculated crude prevalence ratios for different ethnic groups in the Washington Heights–Inwood sample. We assumed that there might be an increase in the number of Hispanic residents relative to white and black residents due to shifts in the proportions of the population during the 1980s. Therefore, the 1980 census data with regard to ethnic groups would underestimate the Hispanic population in the community and overestimate the white population. Because 1990 census data were not available for these comparisons, we corrected for this by estimating the current ratio of the three ethnic groups in the community from data available to us through Medicare registration in 1989 and through our own survey of more than 2500 subjects participating in a community-based study of neurologic disorders. Based on data from these sources, of individuals older than 60 years, 35.3% were black, 37.4% were Hispanic, and 21.3% were white. The overall crude prevalence ratios for blacks was 107.3 per 100 000, for Hispanics was 521.6 per 100 000, and for whites was 1176.8 per 100 000. We did not standardize these estimates because of the uncertainty of the denominator information. Therefore, any comparison between ethnic groups at this time would be misleading. We anticipate age-specific denominator information by ethnic group to be available in the spring of 1992.

The comparison of prevalence in men and women indicated a 73% increase in the standardized prevalence for PD with and without dementia for men in nearly every age group. There was an 87% increase in the standardized prevalence of PD with dementia in men (Table 4).

Parkinson's Disease With Dementia

The overall crude prevalence of PD with dementia was 41.1 per 100 000, and the crude prevalence for those individuals older than 35 years was 90.8 per 100 000 (Table 2). The age-specific prevalence of PD with dementia also increased with age, parallel to the increase in PD overall, as noted in Table 2, from zero per 100 000 for those younger than 50 years to 787.1 per 100 000 older than 80 years. The standardized prevalence ranged from 5.3 per 100 000 for those between ages 35 and 64 years to 62.5 per 100 000 for those older than 75 years (Table 5). The standardized rate ratio for dementia was 0.39 overall, as noted in Table 5. Demented patients were older than their nondemented peers, but duration of motor manifestations was identical (Table 1). To compare the prevalence of PD with demen-

Table 3.—Comparison of Standardized, Age-Specific Prevalence Ratio of Parkinson's Disease in New York, Mississippi, and the United Kingdom*

Age Group, y	Washington Heights–Inwood†	Mississippi and United Kingdom	Standardized Rate Ratio
	Copiah County, Miss (6)		
40-64	39.8	93.0	0.43
65-74	43.2	87.9	0.49
75 +	106.8	105.3	1.01
Total	191.2‡	286.3‡	0.66
	Northhampton, UK (32)		
<50	1.7	2.2	0.78
50-59	4.1	8.2	0.50
60-69	20.1	24.4	0.83
70-79	29.9	47.9	0.62
>80	30.9	34.9	0.88
Total	86.9‡	117.8‡	0.78

*Data are standardized to the US census estimate for 1988 (US Department of Commerce[31]).
†Washington Heights–Inwood is a community in Manhattan, NY.
‡Data are per 100 000.

Table 4.—Comparison of Standardized Prevalence Ratio for Parkinson's Disease (PD) With and Without Dementia by Gender

	PD in Men*		PD in Women*			
Age Group, y	Total	Dementia Only	Total	Dementia Only	SRR, Total†	Men/Women With Dementia Only
<50	1.2	0	2.2	0	0.55	0
50-59	8.5	1.2	0.8	0	9.50	0
60-69	33.1	9.6	12.1	1.7	2.73	5.68
70-79	33.7	11.2	27.7	7.8	1.21	1.43
>80	42.4	28.8	25.5	17.7	1.66	1.63
Total	119.0	50.9	68.5	27.2	1.73	1.87

*Data are per 100 000.
†SRR indicates standardized rate ratio.

Table 5.—Standardized Rate Ratio of Dementia in Parkinson's Disease (PD): Washington Heights–Inwood*

Age Group, y	Standardized Prevalence of PD†	Standardized Prevalence of PD and Dementia†	Standardized Rate Ratio (PDD‡ to PD)
35-64	41.1	5.3	0.12
65-74	43.2	8.2	0.19
75+	106.8	62.5	0.59
Total	191.2	76.0	0.39

*Data are based on US census estimates for 1988. Washington Heights–Inwood is a community in Manhattan, NY.

†Data are per 100 000.

‡PDD indicates PD with dementia.

tia with that of clinically diagnosed Alzheimer's disease, we used the age-specific prevalence ratios from the Eastern Baltimore Mental Health Survey.[33] We found a standardized rate of clinically diagnosed Alzheimer's disease in that study to be 550 per 100 000 compared with the standardized rate of PD with dementia in our study of 70.7 per 100 000.

COMMENT

We found that the age-specific prevalence ratio of PD increases dramatically with age, as has been reported by other investigators.[1-3,6,32] Furthermore, we believe our study to be one of the few population-based estimates of dementia in patients with PD. The overall frequency of dementia was 41.3%, much higher than expected based on earlier studies.[7-13] The proportion of patients with dementia also increased with age, as did the age-specific prevalence of PD with dementia. However, the standardized rate ratio for clinically diagnosed Alzheimer's disease was still nearly eight times that for PD with dementia in our investigation.

We confirmed the increased prevalence of PD in men relative to women and found a similar relationship for PD with dementia. Our data regarding the prevalence of PD in each ethnic group suggests that whites are more frequently affected than are either blacks or Hispanics, but this was based on estimates of the distribution of each ethnic group and requires confirmation when appropriate data are available from the 1990 census. Moreover, any differences in prevalence should be confirmed with incidence data to reduce "prevalent case bias."[31] As with any prevalence or cross-sectional investigation, our collected data should be interpreted with caution.

How Complete Was Case Ascertainment in the Washington Heights–Inwood Community?

Because the community is a relatively small geographic area with a single hospital in the region, we believe that the sample represents a nearly complete sample. Our estimate may be lower than that in Copiah County[6] and Northhampton[32] because we used very strict criteria for the diagnosis of PD. Still, our estimate of prevalence was similar to those of studies that used different methods of case ascertainment.[1,6,32] During the course of our study, we were fortunate to have access to a survey of 700 elderly (older than 65 years) members of our target community who were receiving home assistance from the Health Resources Association. Of the 28 cases of PD identified in that survey, only three patients were previously unknown to us. This suggests that our case-ascertainment in that particular region of the community was as complete as was possible in an urban area. We also reviewed clinic records from the adjacent community of Harlem and found only two eligible cases for our study.

Our estimate of the prevalence of PD was somewhat lower than expected based on published rates in the studies from Northhampton[32] and Copiah County,[6] except in the older age groups. This may reflect differences in methods of recruitment as well as our stricter criteria for the diagnosis of PD.

We observed fewer cases of PD among Hispanics and blacks than among whites. The prevalence ratios may "artificially" differ among the three ethnic groups because of the apparent change in the proportions each group represents in the current population.

Was There a Selection Bias in the Identification of Cases?

We cannot identify a systematic bias in the identification of cases in our study. Patients were identified during a 2½-year period. It is possible that patients with more advanced illness were more easily identified by the methods we used, which would have increased the number of patients with dementia. However, we have no indication that this occurred, because all cases were identified with similar methods of surveillance.

Was the Definition of Parkinson's Disease and Dementia Adequate and Appropriate?

According to Rajput et al,[34] the accuracy of a clinical diagnosis of PD may be as low as 76%, which would make epidemiologic studies difficult. Rajput et al also noted that this figure improved when patients were followed up for a period of 5 years or more[34] and when multiple examiners were used. By requiring two defining features, we were assured of the identification of "typical" cases, although we may have missed subtle or very mild cases of idiopathic PD. We believe that we were able to exclude essential tremor and secondary forms of parkinsonism, which may also explain why our overall prevalence was lower than that in the other two studies cited, because their criteria were not as strict. When the diagnosis was in question, the other neurologists participating in the study were asked to examine the patient, and a consensus was reached.

The diagnosis of dementia is difficult in our community because the educational level varies considerably, and educational level may affect performance on neuropsychological tests. We used a two-stage approach to the diagnosis. First, the neurologist made a decision based on the medical history, the ability to perform activities of daily living, the results of a neurologic examination, and a brief assessment of mental status. Second, the neuropsychological testing was performed on the same date but independently. The battery of neuropsychological tests had been developed and tested in the community before its application in this project.[27] All information derived from these interviews was used in a consensus conference attended by all investigators to determine the final diagnosis. To reduce education bias, our diagnostic criteria for dementia required that a patient exhibit impairment in performing the activities of daily living that were directly related to cognitive decline. A patient who performed poorly on neuropsychological tests but was able to function independently was not considered to be demented. Thus, while we may not have fully eliminated bias in diagnoses with regard to dementia, we believe that we reduced bias to a minimum.

How Common Is Dementia in Parkinson's Disease?

In 1984, Brown and Marsden[13] challenged colleagues by positing that the frequency of dementia in the majority of studies published at that time had been overestimated. They found inconsistencies in the criteria for the diagnosis of PD and dementia and identified a number of potential problems that could obscure the diagnosis of dementia in PD. Their review of investigations performed during the last 60 years indicated an estimate of between 35% and 90%, but they intimated that when *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria[28] for dementia were applied, a lower estimate of 15% would better reflect the actual frequency of dementia. Their report was supported by subsequent studies.[35,36]

Strict criteria for PD and for dementia would improve the accuracy of estimates of their frequency. In addition, unless the population from which patients are selected is specified, prevalence estimates might simply reflect a selection bias from a particular hospital or clinic. In the single community-based study, Sutcliffe[32] found an 11% prevalence rate for dementia in PD in Northhampton but failed to use precise diagnostic criteria.

Rajput et al[3] found the cumulative probability of patients with PD developing dementia to be 21.1% compared with 5.7% for the healthy controls in a retrospective chart review. In our own clinic- and hospital-based investigation,[9,37] the cumulative risk of dementia in patients with idiopathic PD was 60% by age 85 years. These investigations need to be confirmed in "population-based" prospective studies.

Parkinson's disease is a common degenerative disease of the nervous system. Our study indicates that it is more frequent in the elderly and progresses dramatically with increasing age. We also found the expected differences in gender and evidence for differences in prevalence in the black and Hispanic populations.

With regard to dementia, we report the first population prevalence ratio for dementia in patients with idiopathic PD: 41.3%. We also confirm earlier work that indicates that PD with dementia is clearly age dependent, and its frequency increases with each decade of life. The prevalent cases with and without dementia differed in age but not duration of illness (motor manifestations). This strongly suggests that age at onset of PD influences the prevalence of dementia. Confirmation of these data awaits studies of incidence rates of PD with and without dementia.

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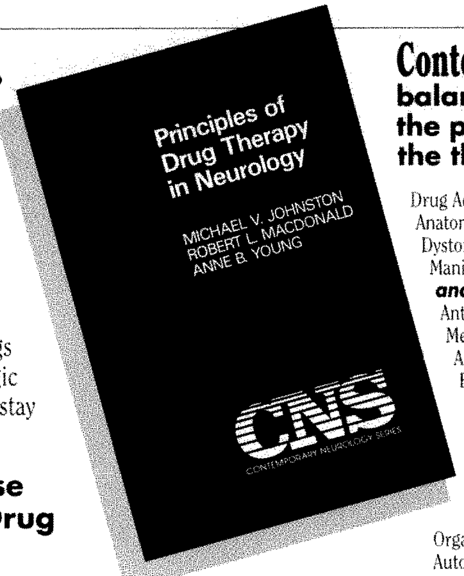
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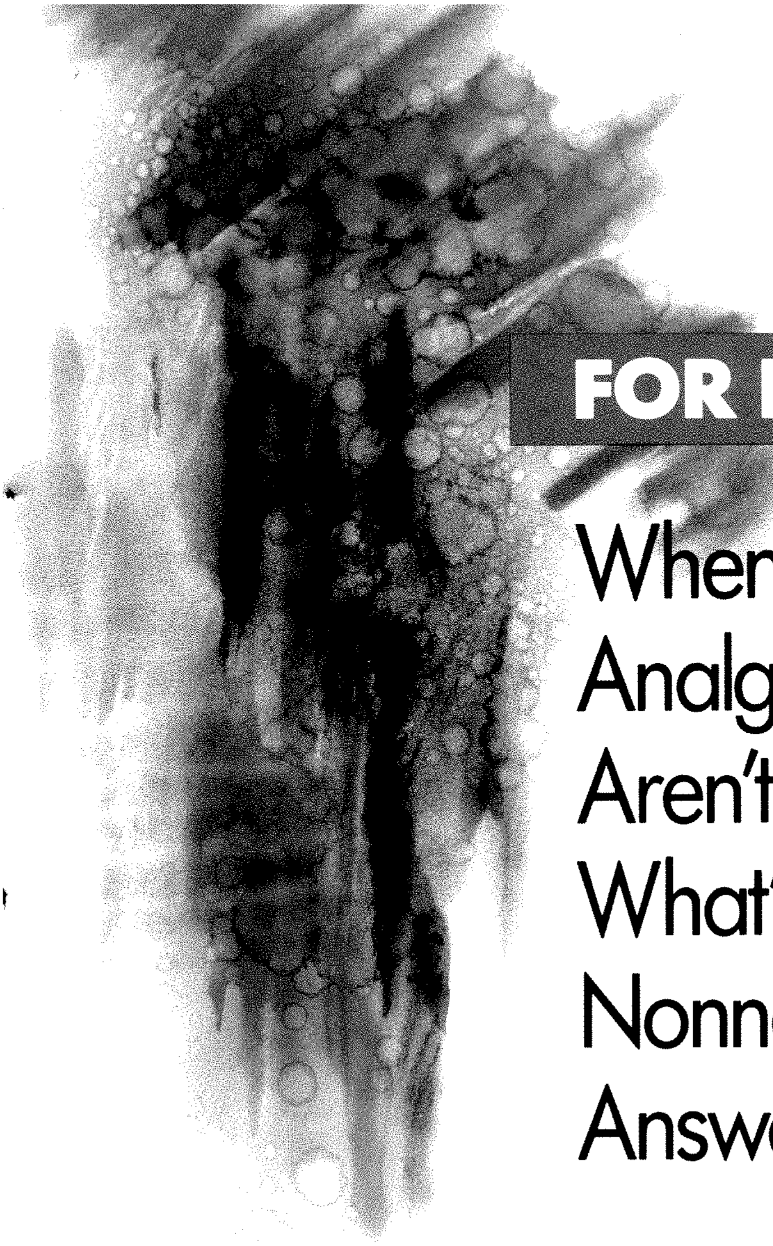

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Onset of action occurs in 15 to 30 minutes following intramuscular administration and persists for 3-4 hours.

Repeated dosage at 1 hour intervals up to 3 hours may be required to obtain maximal effect.

INDICATIONS

As therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so-called "histaminic cephalalgia" when rapid control is desired or when other routes of administration are not feasible.

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Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy. Hypersensitivity.

ADVERSE REACTIONS

Numbness and tingling of fingers and toes, muscle pains in the extremities, weakness in the legs, precordial distress and pain, transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

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DHE-0192-01 1/92

DOSAGE AND ADMINISTRATION

For vascular headache, 1 mL intramuscularly at first warning sign of headache, repeated at 1 hour intervals to a total of 3 mL. Optimal results are obtained by titrating the dose for several headaches to find the minimal effective dose for each patient and this dose should then be employed at onset of subsequent attacks. Where more rapid effect is desired, the intravenous route may be employed to a maximum of 2 mL. Total weekly dosage should not exceed 6 mL.

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Plasma Vitamin B_{12} Level as a Potential Cofactor in Studies of Human Immunodeficiency Virus Type 1–Related Cognitive Changes

Richard S. Beach, MD, PhD; Robert Morgan, PhD; Frances Wilkie, PhD; Emilio Mantero-Atienza, MD, PhD; Nancy Blaney, PhD; Gail Shor-Posner, PhD; Ying Lu, PhD; Carl Eisdorfer, MD, PhD; Marianna K. Baum, PhD

• Studies of cognitive function in subjects with human immunodeficiency virus type 1 (HIV-1) infection who remain relatively asymptomatic (ie, Centers for Disease Control stages II and III) have provided widely variable estimates of cognitive impairment. In view of the finding that approximately 25% of asymptomatic HIV-1–infected subjects demonstrate either marginal or overt vitamin B_{12} deficiency, we have investigated plasma vitamin B_{12} status as a potential cofactor in studies of HIV-1–related cognitive impairment. When cognition was assessed in asymptomatic (Centers for Disease Control stages II and III) HIV-1–infected participants taking into consideration vitamin B_{12} status, those subjects with low plasma vitamin B_{12} levels (<180 pmol/L) performed more poorly than did those with normal (≥180 pmol/L) vitamin B_{12} status on specific measures of information processing speed and visuospatial problem-solving skills. These findings suggest that concurrent vitamin B_{12} deficiency may be a cofactor in subtle cognitive changes observed in the asymptomatic stages of HIV-1 infection. These differences in prevalence of low plasma vitamin B_{12} levels may help to explain differences among studies in the proportion of HIV-1–infected subjects showing cognitive impairment.

(*Arch Neurol.* **1992;49:501-506**)

Infection with the human immunodeficiency virus type 1 (HIV-1) is frequently accompanied by a dementing illness, commonly referred to as the acquired immunodeficiency syndrome (AIDS) dementia complex. The AIDS dementia complex involves abnormalities in cognition, behavior, and motor functions.[1] Although the AIDS dementia complex occurs primarily during the symptomatic stages (Centers for Disease Control [CDC] stage IV) of HIV infection,[2,3] it may be the first symptom of AIDS in up to 10% of patients.[4] A number of investigations,[5-11] including those by our group,[12] have shown cognitive changes during the asymptomatic stages (CDC stages II and III) of HIV-1 infection, with the cognitive alterations primarily in information processing speed and certain aspects of verbal memory. Nonetheless, the estimated prevalence of cognitive abnormalities in CDC stages II and III HIV-1 infection ranges from 6% to 50%.[5,13-15] Variation in the estimates of cognitive abnormalities in asymptomatic HIV-1–seropositive subjects may reflect differences in both the definition of cognitive impairment and the nature of the tasks employed to assess cognitive function. Finally, such differences in the prevalence estimate of cognitive abnormalities in earlier stages of HIV-1 infection may vary with specific subject characteristics.[16-18]

One factor that may influence the neuropsychological status in subjects infected with HIV-1 appears to be vitamin B_{12} status. Deficiency of vitamin B_{12} has been associated with a wide variety of neurological, psychiatric, and cognitive alterations in a number of clinical settings.[19-22] Furthermore, vitamin B_{12} deficiency was observed in 20% of HIV-1–infected subjects referred for neurological evaluations and was associated with both peripheral neuropathy and myelopathy.[22] Of particular interest, recent studies have revealed that not only patients with CDC stage IV HIV-1 infection[22-24] but also relatively asymptomatic (ie, CDC stages II and III) HIV-1–infected subjects are frequently deficient in vitamin B_{12}, as reflected by low plasma vitamin B_{12} levels.[22-25] We recently reported evidence of cognitive inefficiency in a subsample of asymptomatic HIV-1–infected homosexual men.[12] Because vitamin B_{12} deficiency had also been observed in many of these subjects, the purpose of the present investigation was to determine if vitamin B_{12} status was related to the cognitive alterations observed in asymptomatic HIV-1 infection.

SUBJECTS AND METHODS

Subjects

Subjects were 64 HIV-1–positive and 14 HIV-1–negative homosexual men between 21 and 45 years of age, participating in a multidisciplinary prospective longitudinal study of HIV-1 infection. The HIV-1 serological status was determined by enzyme-linked immunosorbent assay confirmed with Western blot technique.[26] Other than having persistent generalized lymphadenopathy, ie, CDC stages II and III at baseline, subjects were asymptomatic.[2] Subjects without persistent generalized lymphadenopathy were required to have $CD4^+$ cell counts of 0.70×10^9/L (700/μL) or less to be admitted to the study. Both HIV-1–seropositive and HIV-1–seronegative subjects were recruited through HIV-1 screening clinics, AIDS service and outreach agencies, and media announcements. Subjects were excluded from this study if they reported a history of head trauma, migraine headaches, major depressive symptoms, use of psychotropic medications, or abuse of illicit drugs (marijuana,

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From the Department of Epidemiology and Public Health (Drs Beach, Morgan, Mantero-Atienza, Shor-Posner, Lu, and Baum), the Center for the Biopsychosocial Study of AIDS (Drs Beach, Morgan, Wilkie, Mantero-Atienza, Blaney, Shor-Posner, Lu, Eisdorfer, and Baum), and the Division of Neonatology (Dr Beach), Broward General Medical Center, Ft Lauderdale, Fla; and the Department of Psychiatry (Drs Mantero-Atienza, Morgan, Wilkie, Blaney, and Eisdorfer), University of Miami (Fla) School of Medicine.

Reprint requests to Division of Neonatology, Broward General Medical Center, 1600 S Andrews Ave, Fort Lauderdale, FL 33136 (Dr Beach).

cocaine, amphetamines, lysergic acid diethylamide, amyl nitrates, or heroin). Because the focus of this report is on cognitive changes in early HIV-1 infection, HIV-1–seropositive subjects were excluded from this sample if they reported or showed on physical examination any symptoms indicating CDC stage IV HIV-1 infection (including stages IV-A and IV-C_2 symptoms previously used for identifying AIDS-related complex).[2] No subjects had taken or were taking antiretrovirals (eg, zidovudine) at the time of the study.

Subjects were grouped according to HIV-1 serological status and vitamin B_{12} status. Plasma vitamin B_{12} levels below 180 pmol/L, including both marginally and overtly deficient levels, were considered low. Plasma vitamin B_{12} levels of 180 pmol/L or greater were considered normal. To allow for appropriate comparisons, three groups were formed: (1) HIV-1–seropositive subjects with plasma vitamin B_{12} levels within normal limits, hereafter referred to as the HIV+/B_{12}nl group; (2) HIV-1–seropositive subjects with low plasma vitamin B_{12} levels, referred to as HIV+/B_{12}def; and (3) HIV-1–seronegative subjects with plasma vitamin B_{12} levels within normal limits, referred to as HIV−/B_{12}nl. None of the HIV-1-seronegative subjects were found to have plasma vitamin B_{12} levels below 180 pmol/L.

Nutritional Measures

All blood was drawn at 8 AM from the antecubital vein on subjects who had fasted for 12 hours, to minimize the influence of the last meal and of diurnal variations, both of which are known to influence plasma measurement of specific nutrients. A tourniquet was used to locate the vein but released during withdrawal of the samples obtained for biochemical determinations. Blood samples were processed and stored at −70°C until ready for analysis. Plasma vitamin B_{12} levels were measured in the Laboratory of the Department of Nutrition Sciences, University of Alabama, Birmingham. Complete blood cell count with a differential cell count was performed by a commercial laboratory by standard methods.

Plasma cobalamin levels, the most abundant form of vitamin B_{12} in plasma, were determined by radioimmunoassay.[27] While such an individual plasma determination may not reflect all of the intricacies of vitamin B_{12} metabolism, it is considered to represent the best single means of assessing overall vitamin B_{12} nutriture.

Cognitive-Neuropsychological Test Battery

Cognition was evaluated utilizing a battery of tests designed to measure a wide range of cognitive processes. Cognitive domains assessed were information processing speeds, visuospatial processes, language, memory, attention, and psychomotor reaction times. Trained psychometrists administered the cognitive tasks. Administration time was approximately 3 hours, spread out over 2 days. Subjects were given frequent rests. This method and the cognitive tasks employed have been described previously.[12]

Information Processing Speed

The time required to process different types of information was assessed by three tests. The Posner Letter Matching Task[28] assessed the speed (in milliseconds) of retrieving highly overlearned name codes from long-term memory. The major variable of interest was the difference between discriminative reaction times to pairs of letters that were physically identical (PI) (eg, *AA, nn*) compared with those that had the same name (name identical [NI]) (eg, *Aa, Nn*). This difference was referred to as the NI-PI variable, with NI reaction times longer than PI reaction times, presumably because of the additional mental processing time required to reach the name level in long-term memory. The Sternberg Short-Term Memory Search Task[29] measured the speed (in milliseconds) of searching short-term memory. On each trial, a memory set, ranging in size from one to four digits, was presented followed by a probe. The task was to determine whether the probe was in the memory set. Reaction time typically increased as a linear function of the number of items in the memory set. The slope of the function is viewed as the memory search speed and the zero intercept is viewed as the nonsearch (eg, encoding, motor) speed. Finally, assessment of information processing speed included the Figural Visual Scanning and Discrimination of Pictures Task,[30] which examined the speed (in seconds) and accuracy in scanning five figures to determine the one matching the prototype on each trial.

Visuospatial Processes

Visuospatial abilities were assessed by the Visual Reproductions from the Wechsler Memory Scale (WMS)[31] utilizing both immediate and 45-minute–delayed recall; by the Wechsler Adult Intelligence Scale–Revised (WAIS-R) Block Design subtest[32]; and by a modified version of the Shepard and Metzler Mental Rotations Task measuring visuospatial problem-solving skills.[33,34]

Language Processes

Language abilities were assessed by the Boston Naming Test,[35] the WAIS-R Vocabulary subtest,[32] the Controlled Oral Word Association test[36] utilizing the letters *C, F,* and *L*, and the WAIS-R Similarities subtest.[37]

Verbal Memory

Verbal memory was assessed by three tests. The Buschke Selective Reminding Test[37] assessed word list learning, utilizing 12 meaningful but unrelated words in up to six trials. The Logical Memory (WMS) test[31] assessed immediate and 45-minute–delayed recall of auditorially presented passages. Finally, Continuous Paired Associates Learning Task was performed under both focused and divided attention conditions utilizing a secondary task paradigm.[38] Both accuracy and response time during paired associate learning were assessed under the focused and divided attention conditions, along with response time to the secondary visual probe task, which was also performed under both conditions.

Attention and Psychomotor Reaction Times

Arousal-attention was examined by Two-Choice Visual Reaction times[12] and by the Visual Probe Reaction Time Task[39] performed as a control condition as well as the distractor in the secondary task paradigm of the Continuous Paired Associates Learning task. This task provided an indirect measure of attentional capacity (ie, effort, resources) during paired associate learning.

Potential Confounds

A major criticism of early studies of cognition in HIV-1 infection is the relative lack of attention given to the possible confounding influence of both substance abuse and subclinical depression and/or anxiety.[16,17] The Profile of Mood States[40] was used in this study to measure self-reported affective states. Previous work within our center[41] indicates that a composite formed from four of the Profile of Mood States scales (Depression, Anxiety, Confusion, and Fatigue) provides a useful summary of psychological distress. As would be expected, this composite correlates highly with both the Depression and Anxiety subscales ($r = .92$ and $r = .89$, respectively) within this sample.

Alcohol use has also been cited as an important potential confound in studies of cognition.[42] Although an effort was made to exclude subjects who abused alcohol from this study, the sample still exhibits a range of mild to moderate drinking. Self-reported use of alcohol was routinely collected as part of the physical examination. Use was coded into five ordered categories: 0, no use; 1, less than one drink per week; 2, one to five drinks per week; 3, five to 10 drinks per week; and 4, more than 10 drinks per week.

Age, years of education, and primary language (English or Spanish) were examined for possible influences on cognitive performance, independent of vitamin B_{12} or HIV-1 status.

Table 1.—Adjusted Mean Information Processing Speeds*

	HIV−/B_{12}nl (n=11)	HIV+/B_{12}nl (n=28)	HIV+/B_{12}def (n=12)
Decoding speed: Posner Letter Matching Task, ms†‡	97.85±69.97	121.44±62.39	205.47±64.11
Visual scanning time§, s	63.07±23.97	68.60±20.80	88.68±21.36
Paired associates response time, ms			
Single task‖	10.78±0.27¶ (1758)	10.63±0.24 (1585)	10.82±0.25 (1808)
Dual task‖	10.74±0.26 (1710)	10.61±0.24 (1563)	10.61±0.25 (1771)
Sternberg Short-Term Memory Search speed slope, ms	77.80±35.30	73.69±31.91	56.84±32.80

*HIV-/B_{12}nl indicates human immunodeficiency virus type 1–seronegative subjects with normal vitamin B_{12} values; HIV+/B_{12}nl, HIV-1–seropositive subjects with normal vitamin B_{12} values; and HIV+/B_{12}def, HIV-1–seropositive subjects with vitamin B_{12} deficiency. Values are mean±SD. Thirteen subjects were missing observations on one or more of the measures included in the multivariate analysis.

†Means adjusted for age, years of education, and depression/anxiety. Multivariate F=2.82, $P<.005$.

‡The comparisons for HIV−/B_{12}nl and HIV+/B_{12}nl both significantly less than HIV+/B_{12}def, $P<.001$.

§The comparisons for HIV−/B_{12}nl and HIV+/B_{12}nl both significantly less than HIV+B_{12}def, $P<.05$.

‖The comparison for HIV−/B_{12}nl significantly less than for both HIV+/B_{12}nl and HIV+/B_{12}def, $P<.05$.

¶Log_2 transformed response time (retransformed means).

Finally, immunological status, as measured by the count of CD4$^+$ lymphocytes, was used as a marker for disease progression and tested for inclusion as a covariable.

Statistical Analyses

Differences in cognitive function among the (1) HIV+/B_{12}nl, (2) HIV+/B_{12}def, and (3) HIV−/B_{12}nl groups were evaluated using a combination of multivariate and repeated-measures analyses of covariance. In each analysis, an overall test of between-group differences among the three groups was performed, followed by paired comparisons if the overall F was significant. An $\alpha=.05$ was used to indicate statistical significance, and $\alpha=.10$ was used as a cutoff for results approaching statistical significance. Not all subjects had data for all of the measures. Since the multivariate analyses require complete data on all measures, the sample size varied slightly across analyses. It should be noted that 13 subjects were missing one or more measures of information processing, generally due to limitations in individual subject's time availability. The subjects who were missing these measures did not differ from the other HIV-1–seropositive subjects on demographic, immunological, or nutritional characteristics. Univariate statistics calculated on the individual information processing measures (to maximize the sample size for each measure) yield the same pattern of differences reported in analyses given in Table 1 (the actual number of subject determinations is listed in each table).

Preliminary analyses were performed to evaluate the relationship between the cognitive measures and possible confounding variables (age, education, primary language, psychological distress, alcohol use, and CD4$^+$ cell count). Each of these factors was expected to demonstrate some level of association with cognitive function. Thus, their inclusion in the analyses as covariates was expected to increase the sensitivity of the between-group analyses by reducing the within-group residual variance (ie, error variance) estimated by the models. The relationships between all covariates and the dependent measures were evaluated before the tests of group differences. Covariates were retained in the models if the P value associated with their independent contribution to the model (eg, controlling for the other covariates) was less than or equal to .10.

RESULTS

Subject Characteristics

The medians, means, and SDs for plasma vitamin B_{12} levels, age, years of education, psychological distress, alcohol use, and CD4$^+$ cell count are presented for each group in Table 2. The average CD4$^+$ cell counts differed between the HIV+/B_{12}nl, HIV+/B_{12}def, and HIV−/B_{12}nl groups, with the HIV−/B_{12}nl subjects showing a higher mean CD4$^+$ cell count ($0.81\pm0.24\times10^9$/L [805±237 cells/μL]) than either of the two HIV-1–seropositive groups ($P\leq.003$ in both cases). The mean CD4$^+$ cell counts for the HIV+/B_{12}def and HIV+/B_{12}nl subjects were quite similar (both $0.55\pm0.33\times10^9$/L [511±266 cells/μL]; $P\geq.20$). The absolute CD4$^+$ count did not show any associations with the cognitive measures used in this study ($P\geq.10$ in all cases) after adjusting for HIV-1 serological status. Both age and education differed across groups (overall $P\leq.04$ and $P\leq.003$, respectively), with the principal differences between the HIV-1–seronegative subjects and the combined groups of HIV-1–seropositive subjects ($P\leq.02$ and $P\leq.001$, respectively, for age and education). These variables are entered as covariates in all analyses. There were no between-group differences in primary language, psychological distress, or extent of alcohol use ($P\geq.20$ in all cases). These measures were tested, as described above, for inclusion in the models. All covariables retained in the final models are indicated in the appropriate tables. In addition, there was no evidence of hematological abnormalities typically used to screen for vitamin B_{12} deficiency in any of the participants in this study with plasma vitamin B_{12} levels below 180 pmol/L. Among these subjects, all measures of mean corpuscular volume were 100 fL or less (90±4 fL), while all hematocrit levels were above 0.36 (0.42±0.04).

Information Processing Speed

As presented in Table 1, there was a statistically significant multivariate between-group difference in the information processing measures (overall multivariate F=2.82, $P\leq.005$), with both the HIV−/B_{12}nl and the HIV+/B_{12}nl subjects showing multivariate differences from the HIV+/B_{12}def subjects ($P\leq.003$ and $P\leq.004$, respectively). There was no significant difference between the HIV−/B_{12}nl and HIV+/B_{12}nl subjects. The between-group differences between the HIV+/B_{12}def vs HIV+/B_{12}nl and HIV−/B_{12}nl groups were most dramatic on the Posner Letter Matching (NI-PI) Task. After adjusting for the covariates included in the final model (age, years of education, and the Profile of Mood States composite scale), the average response time for the HIV+/B_{12}def group was 205.47±64.11 vs

Table 2.—Demographics and Covariates*

Measure	HIV − /B_{12}nl (n = 14)	HIV + /B_{12}nl (n = 36)	HIV + /B_{12}def (n = 14)
Age, y†	38.50 ± 10.20	33.78 ± 7.03	31.00 ± 5.72
Education, y‡	16.71 ± 1.49	14.83 ± 1.80	14.64 ± 2.06
$CD4^+$ cell count, × 10^9/L (cells/μL)‡	0.81 ± 0.24 (805 ± 237)	0.50 ± 0.27 (510 ± 266)	0.47 ± 0.33 (472 ± 331)
Distress composite	32.71 ± 25.05	39.33 ± 22.46	39.62 ± 21.78
Alcohol use, g/wk	54 ± 37	50 ± 41	58 ± 42
Plasma vitamin B_{12}, pmol/L§	360 (310-390)	280 (240-450)	130 (110-160)
Primary language			
English	11 (0.79)	26 (0.72)	12 (0.86)
Spanish	3 (0.21)	10 (0.28)	2 (0.14)

*Abbreviations are as in Table 1. Values are mean ± SD, except for plasma vitamin B_{12} level; median (25th-75th percentile); and primary language, frequency (proportion of group).

†$.019 < P < .05$.

‡$.001 < P < .01$.

§$P < .001$.

121.44±62.39 milliseconds for the HIV+/B_{12}nl group and 97.85±68.97 milliseconds for the HIV−/B_{12}nl group ($P \leq .001$ for both comparisons). Differences on the Figural Visual Scanning and Discrimination of Pictures Task were also significant. The average adjusted response times for the HIV+/B_{12}def group were 88.68±21.36 vs 68.60±20.8 milliseconds ($P \leq .01$) and 63.07±22.97 milliseconds ($P \leq .02$) for the HIV+/B_{12}nl and HIV−/B_{12}nl groups, respectively. The HIV+/B_{12}nl and HIV−/B_{12}nl groups were not different on either of these tasks. The mean response times from the Continuous Paired Associates Learning paradigm, both single and dual tasks, showed only a trend that approached statistical significance ($P \leq .06$ and $P \leq .07$ overall, respectively). Nevertheless, in both tasks, the HIV+/B_{12}def group did show slower average responses than the HIV+/B_{12}nl group ($P \leq 0.04$ for both the single and dual tasks). Interestingly, the HIV−/B_{12}nl group also showed slower average response times than the HIV+/B_{12}nl group under both conditions ($P \leq .05$ for both the single and dual tasks). Thus, the pattern of between-group differences on the Continuous Paired Associates Learning primary task was different than that seen on the NI-PI or the Figural Visual Scanning and Discrimination of Pictures Task measures. While the HIV+/B_{12}nl subjects still performed better than the HIV+/B_{12}def subjects, the HIV+/B_{12}def subjects and the HIV−/B_{12}nl subjects showed comparable response times. The slope measure from the Sternberg Short-Term Memory Search Task was nonsignificant with regard to either HIV-1 serological status or plasma vitamin B_{12} level ($P \geq .20$).

A follow-up test of a condition (single vs dual task)-by-group interaction on the Continuous Paired Associates Learning Task measures showed no statistically significant fluctuation in the between-group differences across the two testing conditions. An overall test of the between-group differences, collapsing across condition, did reach overall significance (overall $P \leq .05$; HIV+/B_{12}nl vs HIV+/B_{12}def, $P \leq .03$). Clearly, this is a restatement of the differences shown in the separate univariate tests for the single and dual task conditions, not an independent confirmation of those differences. Nonetheless, it suggests that there is a single, between-groups effect for the Continuous Paired Associates Learning Task.

Visuospatial Processes

In addition to the measures of information processing, marginally significant differences were observed on a modified version of the Shepard and Metzler Mental Rotations Task (Table 3). Typically, the number correct declines with increasing angle of rotation. While the HIV+/B_{12}nl subjects start from a lower baseline performance (ie, a lower number of correct answers on the easiest set of tasks) and show a decline in performance comparable with that observed in HIV−/B_{12}nl subjects with initial increasing difficulty of task, their performance is more similar to that observed in the HIV−/B_{12}nl subjects on the most difficult angle of rotation. In contrast, the HIV+/B_{12}def subjects showed fewer correct responses initially and subsequently a steeper decline in performance with increasing level of difficulty (HIV+/B_{12}nl vs HIV+/B_{12}def, $P \leq .02$). Moreover, at the most difficult angle of rotation, HIV+/B_{12}def subjects performed substantially more poorly than either the HIV−/B_{12}nl subjects ($P \leq .03$) or the HIV+/B_{12}nl subjects ($P \leq .01$).

No significant between-group differences were observed on the basis of HIV-1 serological status or plasma vitamin B_{12} status on the Visual Reproductions subscale of the WMS or on the Block Design subtest of the WAIS-R (Table 3).

Other Cognitive Measures

There were no overall group differences found on the measures of language processes (Boston Naming, WAIS-R Vocabulary, Controlled Oral Word Association Test, and WAIS-R Similarities), the measures of verbal memory (WMS Logical Memory and The Buschke Selective Reminding Test measures: Consistent Long-Term Retrieval [CLTR], Long-Term Retrieval [LTR], Long-Term Storage [LTS], and Short-Term Retrieval [STR]). In addition, no between-group differences were found on the measures of attention and psychomotor reaction time (the Visual Probe Reaction Time Task, performed as a control condition as well as a secondary task in the Continuous Paired Associates Learning Task and the Two-Choice Visual Reaction Time Task).

Table 3.—Adjusted Mean Visuospatial Scores*

	HIV−/B_{12}nl (n=13)	HIV+/B_{12}nl (n=35)	HIV+/B_{12}def (n=14)
WMS Visual Memory			
Immediate recall	11.73±2.47	10.86±2.25	11.30±2.31
Delayed (45-min) recall	10.51±3.97	9.25±3.61	8.85±3.71
WAIS-R Block Design	12.98±2.69	11.29±2.48	11.61±2.52
Mental Rotations, No. correct			
Task 1	15.36±4.36	12.99±4.25	12.79±4.45
Task 2	14.67±4.05	12.20±3.96	11.45±4.15
Task 3	13.57±4.642	12.76±4.48	9.32±4.75

*WMS indicates Wechsler Memory Scale; WAIS-R, Wechsler Adult Intelligence Scale–Revised; other abbreviations are as in Table 1. Values are mean ± SD. The WMS means were adjusted for age, years of education, and depression/anxiety; WAIS-R means, for age, years of education, depression/anxiety, and primary language; and the modified version of the Shepard and Metzler Mental Rotations Task means, for age, years of education, primary language, and alcohol use.

†Between-group $F=2.61$, $P \leq .09$; between-group task $F=2.32$, $P \leq .07$.

‡HIV−/B_{12}nl significantly greater than HIV+/B_{12}nl and HIV+/B_{12}def groups, $P<.10$.

§HIV−/B_{12}nl and HIV+/B_{12}nl both significantly greater than HIV+/B_{12}def group, $P<.05$.

COMMENT

The present study assessed the potential role of low plasma vitamin B_{12} levels in the interaction between HIV-1 infection and cognitive function. Those areas of cognitive function that showed the strongest relationship with plasma vitamin B_{12} levels in the setting of HIV-1 infection were specific areas of information processing speed and visuospatial problem-solving abilities. These differences did not appear to be explained by self-reported alcohol use, measures of psychological distress, age, education, or native language, or by the participant's immunological status as measured by $CD4^+$ lymphocyte count.

Information processing speed is one of the primary areas of cognitive function in which changes have been identified in asymptomatic HIV-1–infected subjects.[10-12] Among the present subjects, vitamin B_{12} deficiency, as reflected by low plasma vitamin B_{12} levels, appeared to account for a significant share of the delay in the speed of retrieving highly overlearned name codes and in the speed of visual scanning and discrimination. Indeed, HIV-1–infected subjects with normal plasma vitamin B_{12} levels performed much like HIV-1–negative subjects on the Posner Letter Matching and Figural Visual Scanning and Discrimination of Pictures time tasks. In contrast, HIV-1–positive subjects with low plasma vitamin B_{12} values scored more poorly than did either of the other two groups, regardless of HIV-1 serological status. This suggests that differences in the estimates of the prevalence of certain cognitive abnormalities may be substantially influenced by the vitamin B_{12} status of the participants. It should be noted, however, that vitamin B_{12} status did not appear to be associated with a generalized slowing in the speed of central processes or in motor speed since it did not distinguish between the groups on the Sternberg Short-Term Memory Search speed, response speed to a visual probe used as a secondary task during paired associates learning, or to Two-Choice Visual Reaction time. However, the tasks that were sensitive to the effects of vitamin B_{12} deficiency were the same information-processing speed tasks that Wilkie and colleagues[12] had previously shown to distinguish between HIV-1–seropositive and HIV-1–seronegative subjects. These results suggest that vitamin B_{12} deficiency could be a contributing factor to slower information processing speeds in asymptomatic HIV-1–infected subjects.

Overtly low plasma vitamin B_{12} levels (ie, <150 pmol/L) have been shown to occur in approximately 10% to 15% of CDC stages II and III HIV-1–infected homosexual males, with an additional 10% to 15% exhibiting marginal vitamin B_{12} deficiency (plasma vitamin B_{12} levels between 150 and 180 pmol/L).[25] Patients diagnosed with stage IV HIV-1 infection have an even higher prevalence of low plasma vitamin B_{12} levels.[22-24] The causative factors related to such plasma vitamin B_{12} deficiency have been found to be multifactorial in nature, eg, lack of intrinsic factor, autoantibodies to intrinsic factor, and mucosal abnormalities, and are different in individual patients. Vitamin B_{12} deficiency, as reflected by low plasma vitamin B_{12} levels, occurs in many clinical settings[43] and has frequently been associated with a wide variety of psychological-psychiatric,[19,20] cognitive,[20] and overt neurological manifestations.[21,22] Many of these patients exhibiting significant neuropsychological abnormalities do not exhibit hematological abnormalities,[44] which have been considered to be a key screening tool for the presence of a low plasma vitamin B_{12} level. None of the patients in the present investigation of HIV-1 infection had evidence of either anemia or increased mean red blood cell volume, consistent with recent findings in other clinical settings.[45] While earlier studies of vitamin B_{12} and neuropsychological function suffered from methodological inconsistencies and an anecdotal nature,[46] more recent investigations have clearly documented the relationship between low plasma vitamin B_{12} levels and a wide variety of neurological and psychiatric manifestations without evidence of hematological abnormalities.[47]

Reciprocal elevation of vitamin B_{12} analogues, as well as accumulation of methylmalonic acid and homocysteine in serum and cerebrospinal fluid,[47] have been suggested as possible mechanisms whereby low plasma vitamin B_{12} levels might cause psychoneurological symptoms without resulting in simultaneous hematological consequences. Whatever the mechanisms, it would appear quite clear, as in other clinical settings, that low plasma vitamin B_{12} levels could potentially complicate neuropsychological sequelae in patients with HIV-1 infection.

While the more severe manifestations, ie, the AIDS dementia complex, reflect multiple neuropsychological abnormalities and generally occur later in the overall disease process, some[5-12] but not all[13-15] investigations have observed subtle changes in memory and information processing in relatively asymptomatic HIV-1–infected subjects. At this time, it is not known whether these earlier, more subtle changes in cognition will subsequently progress to HIV-1–associated dementia. Moreover, the precise cause of such cognitive and behavioral abnormalities remains unknown. Our findings indicate an association between vitamin B_{12} deficiency and impaired information processing speed and visuospatial problem-solving abilities. These results emphasize the need to determine the long-term effects of vitamin B_{12} deficiency and to investigate mechanisms through which HIV-1 infection, vitamin B_{12} deficiency, and cognitive function may be related. Preliminary results indicated that even late-stage neurological deficits that develop in HIV-1–infected subjects may be reversible with cyanocobalamin therapy.[22] The present results emphasize the potential importance of trials of early clinical intervention in the possible prevention of such early-onset cognitive changes in select subjects with HIV-1 infection.

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POSTHERPETIC NEURALGIA

There Are Many Words To Describe The Pain.

STABBING
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SHARP
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PIERCING
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And One For Treating It.

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When patients describe the "hurt" of postherpetic neuralgia (PHN), they use a wide range of words to describe a pain that is often intractable and difficult to treat. Zostrix® (Capsaicin 0.025% w/w) Cream provides an effective topical treatment that alleviates intense pain in most PHN patients.

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SAFE

No known interactions with systemic medications commonly prescribed for geriatric patients.

Topical Zostrix Works Where It Hurts

DESCRIPTION

Zostrix Cream contains capsaicin, 0.025% w/w, in an emollient base containing benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, polyoxyethylene stearate blend, purified water, sorbitol solution and white petrolatum. Capsaicin is a naturally occurring substance derived from plants of the Solanaceae family with the chemical name trans-8-methyl-N-vanillyl-6-nonenamide. Capsaicin is a white crystalline powder with a molecular weight of 305.4. It is practically insoluble in water but very soluble in alcohol, ether and chloroform.

ACTION

Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemomediator of pain impulses from the periphery to the central nervous system. In addition, substance P has been shown to be released into joint tissues and activate inflammatory mediators involved with the pathogenesis of rheumatoid arthritis.

INDICATION

Zostrix is indicated for the temporary relief of peripheral neuralgias such as the pain following shingles (herpes zoster). Zostrix is also indicated for the temporary relief of the pain associated with rheumatoid arthritis and osteoarthritis.

WARNINGS

FOR EXTERNAL USE ONLY. Avoid contact with eyes and broken or irritated skin. Do not bandage tightly. If condition worsens, or does not improve after 28 days, discontinue use of this product and consult your physician. **Keep this and all drugs out of the reach of children.** In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

DIRECTIONS

Adults and children 2 years of age and older: Apply Zostrix to affected area 3 to 4 times daily. Transient burning may occur upon application, but usually disappears in 72 hours. Application schedules of less than 3 to 4 times a day may not provide optimum pain relief and the burning sensation may persist. **Wash hands immediately after applying Zostrix.**

HOW SUPPLIED

1.5 oz tube (NDC 52761-552-45)
3.0 oz tube (NDC 52761-552-85)

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Early Seizures After Acute Stroke

Risk of Late Seizures

Christine J. Kilpatrick, MD, FRACP; Stephen M. Davis, MD, FRACP; John L. Hopper, MSc, PhD; Stephen C. Rossiter

• The prognosis of early seizures after stroke is controversial. We assessed the incidence of late seizures in 31 patients with early seizures complicating acute stroke and compared this with the incidence of late seizures in 31 matched patients with stroke without early seizures. Ten (32%) of 31 patients with early seizures had late seizures during a mean follow-up period of 26 months. Only three (10%) of 31 patients without early seizures had late seizures during the follow-up period of 28 months, a significantly lower incidence than in patients with early seizures. The risk of seizure recurrence in patients with early seizures did not correlate with stroke type or lesion size as imaged on the computed tomographic scan. We conclude that early seizures are not benign and are associated with a significant risk of seizure recurrence.

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The relationship between cerebrovascular disease and seizures has been recognized since 1864, when Hughlings Jackson[1] reported partial seizures complicating embolic stroke. We have previously reported a 4.4% incidence of early seizures in a large prospective study of acute stroke.[2] Although the occurrence of epileptic seizures complicating acute stroke is well recognized, the risk of recurrent or late seizures in these patients is controversial.

Previous studies have suggested that early seizures (within 2 weeks of stroke onset) are benign and unassociated with a high risk of late epilepsy.[3-7] Louis and McDowell[4] reported seizure recurrence in only two of 33 patients with early seizures complicating nonembolic cortical infarction. More recent studies, however, have reported a higher incidence of seizure recurrence in this patient population.[8-10] No previous study has compared the incidence of late seizures in patients with and without early seizures from the same population of patients with acute stroke.

This study assessed the incidence of late seizures in patients whose acute stroke was complicated by early seizures and compared this with the incidence of late seizures in patients with stroke without early seizures.

SUBJECTS AND METHODS

We previously described 44 patients with early seizures complicating acute stroke or transient ischemic attacks.[2] These patients were prospectively identified from 1000 consecutive patients presenting to the Royal Melbourne (Australia) Hospital Stroke Service between February 1987 and July 1989.

Fifty-five percent of these 1000 patients were male, aged 66±15 years (mean±SD). The gender of patients with early seizures was the same as in the patients without seizures, and no significant difference was noted in the age of the patients with early seizures (62±10 years) and those without seizures.

All 44 patients had a cerebral computed tomographic (CT) scan. To delineate stroke type and pathogenesis further, other investigations, including magnetic resonance imaging, duplex Doppler, angiography, echocardiography, and electroencephalography, were performed where appropriate.

Of the 44 patients, four had seizures complicating transient ischemic attacks, and nine patients died during the admission for acute stroke. Of the 31 patients with early seizures complicating stroke who survived the admission for acute stroke, 19 had cortical infarction, eight had lobar or extensive hemorrhage, and four had subarachnoid hemorrhage. Twenty patients had partial, 16 had simple partial, and four had secondarily generalized seizures. Eleven patients had tonic-clonic seizures.

Information regarding seizure recurrence in these 31 patients was sought retrospectively from hospital medical records, information from the local physician, and telephone or direct contact with patients or their relatives. No patient was unavailable for follow-up, and in all patients the length of follow-up, including those patients who had died following discharge from the hospital, was recorded. Late seizures were defined as seizures occurring following discharge. In each case, seizure type, number of seizures, and time from early seizure to late seizure was noted. In no patient was the occurrence of a late seizure secondary to recurrent stroke.

To assess the role of early seizures in predisposing to late seizures, we assessed the incidence of late seizures in 31 patients whose stroke was not complicated by early seizures. These patients were randomly selected from the initial 1000 patients excluding the 44 patients with early seizures, from which the 31 patients with early seizures were prospectively identified. Patients were matched for age within a decade, sex, and stroke type (cortical infarction, lobar or extensive hemorrhage, subarachnoid hemorrhage) to those patients with early seizures. As we had previously found an association between pathogenesis of lobar hemorrhage and the incidence of early seizures, patients

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Correlations Between Stroke Type and Early and Late Seizures

Stroke Type of Patients With Early Seizures (n)	Stroke With Early and Late Seizures	Stroke Type of Matched Patients Without Early Seizures	Stroke Without Early and Late Seizures
Cortical infarct (19)	5*	19	0
Lobar hemorrhage (8)	5*	8	2
Subarachnoid hemorrhage (4)	0	4	1
Total (31)	**10†**	**31**	**3†**

*No correlation between stroke type of patients with early seizures and the incidence of late seizures ($P<.1$).
†Late seizures significantly more frequent in patient with early seizures ($P<.02$).

with lobar hemorrhage were matched for stroke pathogenesis.[2] Information regarding occurrence of late seizures in these 31 patients without early seizures was sought in the same manner as for patients with early seizures.

We also assessed the value of anticonvulsant drugs in preventing seizure recurrence in patients with early seizures by assessing the incidence of late seizures in patients with early seizures who were treated with anticonvulsant drugs and comparing this with the incidence of late seizures in patients with early seizures who did not receive anticonvulsant therapy. In addition, the role of surgery in patients with intracerebral hemorrhage as a predisposing factor to the development of late seizures was evaluated by assessing the incidence of late seizures in patients with intracerebral hemorrhage, who had surgery, and comparing this with the incidence of late seizures in patients whose hemorrhage was not treated surgically. To assess whether the incidence of late seizures in patients with early seizures correlated with the size of the lesion on the cerebral CT scan, the lesion imaged on the CT scan was measured in 27 patients with either cerebral infarction (19) or intracerebral hemorrhage (eight) and early seizures. Lesions were defined as small or nonvisualized (<10 mm, fewer than five slices), or large (>10 mm, five slices, complete vascular territory).[2]

STATISTICAL METHODS

Differences in crude proportions were assessed by χ^2 test for independence by 2×2 tables. The analysis of matched data, performed so as to adjust for age, sex, and stroke type, was performed by testing if the distribution on discordant pairs was different from a random allocation by calculating the binomial distribution with $P=.5$. Time to late seizures was compared by survival analysis techniques, using the Mantel-Haenszel Log-Rank test.[11]

RESULTS

Ten (32%) of the 31 patients with early seizures had late seizures during a mean follow-up period of 26 months. No correlation was noted between stroke type and risk of late seizures in patients with early seizures (Table). Five of the 19 patients with cortical infarction and early seizures had late seizures, compared with five of the eight patients with lobar hemorrhage and early seizures, a difference that did not reach statistical significance ($P<.1$). None of the patients with subarachnoid hemorrhage and early seizures had further seizures.

In nine of the 10 patients, the late seizures were of the same type as the early seizures. The type of early seizure did not predict seizure recurrence. The time from early seizure to late seizure varied from 3 months to 2.5 years, with a mean of 12 months. One of the 10 patients had a history of late-onset epilepsy of unknown cause.

Seven of these 10 patients were taking phenytoin sodium when the seizure recurred. One patient had a seizure 1 week after stopping phenytoin use. In all but one patient, seizures were isolated. In six of the 10 patients, further seizures did not occur following commencement of anticonvulsant medication or alteration of existing anticonvulsant therapy. Four patients had recurring seizures, albeit infrequently. Only one patient had poorly controlled epilepsy.

Of the 31 patients with early seizures who survived the admission for acute stroke, 21 were discharged receiving anticonvulsant medication. Prophylactic anticonvulsant therapy did not seem to prevent seizure recurrence. Seven of these 21 patients had late seizures, and three of the 10 patients not receiving anticonvulsant medication had late seizures.

Of the 27 patients with either cortical infarction (19) or lobar hemorrhage (eight) and early seizures, 14 had large lesions as imaged on the cerebral CT scan, and 13 patients had small lesions. Lesion size did not correlate with the risk of seizure recurrence. Of the 14 patients with large lesions, seven had late seizures, compared with three of the 13 patients with small lesions ($P>.1$).

Late seizures were significantly more common in patients whose stroke was complicated by early seizures (Table). Of the 31 patients without early seizures, three (10%) had late seizures during a mean follow-up period of 28 months, a significantly lower incidence than in the patients with early seizures ($P<.05$). When 31 patients with early seizures were matched for age, sex, and stroke type with 31 patients without early seizures, there were nine pairs discordant for late seizures. In eight of these nine pairs, the patient with late seizures also had early seizures ($P<.02$). (If the patient with a history of late-onset epilepsy of unknown cause was excluded, then $P=.05$ and $P<.04$.) In two patients, the stroke was due to a lobar hemorrhage; one patient had a subarachnoid hemorrhage 6 months earlier, and the seizure occurred in the postoperative period following the clipping of an intracranial aneurysm. Each patient had a single tonic-clonic seizure, and ready control was achieved with anticonvulsant treatment.

The time to late seizures in patients with and without early seizures complicating acute stroke was compared. The time to late seizures was shorter in patients with early seizures ($P<.02$), with one third of these patients having late seizures within 2 years of stroke onset.

The risk of late seizures in patients with cerebral hemorrhage did not relate to surgical or conservative treatment. Of the 16 patients with lobar hemorrhage (eight patients with early seizures and eight patients without early seizures), nine had surgery and seven were treated conservatively. Of the nine patients with surgery, three had late seizures, and of the seven patients without surgery, four had late seizures.

COMMENT

In this study, late seizures occurred in 32% of patients with early seizures, compared with only 10% of patients whose stroke was not complicated by early seizures. This finding suggests that early seizures are not benign as previously proposed and are associated with a significant risk of late seizures. Risk of seizure recurrence did not correlate with stroke type or lesion size. Although anticonvulsant therapy did not seem to reduce the risk of seizure recurrence, the number studied was small, patients were not randomized to treatment and nontreatment groups, and some uncertainty regarding the use of anticonvulsant medication was noted.

In contrast to our findings, Louis and McDowell[4] reported a low incidence of seizure recurrence in patients with early seizures complicating nonembolic cortical infarction and suggested that early seizures had a better prognosis than late seizures, which tended to recur. Similar conclusions were reached by others.[5-7] In a study of cerebral embolization, Meyer et al[5] reported recurrent seizures following discharge in only two of 18 patients with early seizures. Similarly, Shinton et al[6] reported no seizure recurrence in five patients with early seizures complicating cortical infarction, and Faught et al,[7] in a retrospective study of primary intracerebral hemorrhage, concluded that early seizures do not predict late seizures, and most patients with early seizures do not suffer chronic epilepsy.

Other studies have not supported these findings. Gupta et al,[8] in a more recent study of cortical infarction and seizures, reported a recurrence rate of 40% in patients with early seizures, and Sung and Chu,[9] in a study of intracerebral hemorrhage and seizures, reported similar findings. Similarly, Hauser et al[10] reported a higher risk of late epilepsy in patients whose stroke was complicated by early seizures. The results of this study demonstrating a high risk of late seizures in patients with early seizures are comparable with these reported findings. None of the previous studies, however, have compared the incidence of late seizures in patients with and without early seizures.

Although patients with early seizures had a high incidence of seizure recurrence, seizures were usually readily controlled. This is consistent with previous reports,[4,8] and some authors have suggested that anticonvulsants are not indicated.[6] We attempted to assess the usefulness of anticonvulsant medication in preventing seizure recurrence in patients with early seizures, but the numbers studied were too small to make conclusions.

It has been assumed that intracranial surgery in patients with intracerebral hemorrhage increases the risk of epilepsy. As in a previously reported study,[7] this study did not confirm this, and, in fact, the actual proportion of patients with late seizures and surgery was less. However, the small number of patients studied and nonrandom allocation of patients to surgery cautions against overinterpretation.

Patients with early seizures complicating acute stroke do have a significant risk of late epilepsy. Contrary to some previous reports, early seizures are not benign and are associated with a high incidence of seizure recurrence.

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Headaches Preceded by Visual Aura Among Adolescents and Young Adults

A Population-Based Survey

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• Clinical descriptions of migraine preceded by visual aura often include a composite of striking and severe symptoms of several attacks in individual patients, but few studies have characterized the spectrum of such attacks. In a population-based telephone survey of 8920 Washington County, Maryland, residents 12 through 29 years old, the attack rate for visual aura headaches during the week prior to the standardized interview was 3.7% in male and 6.1% in female subjects. Among female subjects, the risk for visual aura headache with tension-type symptoms increased with age, whereas the risk for visual aura headache without tension symptoms decreased with increasing age. No clear age-related patterns were observed among male subjects for either type of aura headache. The severity of visual aura headache with and without tension symptoms increased with age among female subjects, but showed an inconsistent pattern among male subjects except for decreasing disability with increasing age. The median interval between the onset of aura symptoms and the onset of headache (aura interval) was 15 minutes in male subjects and 25 minutes in female subjects, with aura intervals longer than 60 minutes reported by 12% of male subjects and 20% of female subjects. In one of the first large population-based studies to characterize the spectrum of visual aura headache, differing age, gender, and subtype patterns were found.

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There are few articles describing the spectrum of headache attacks preceded by visual aura symptoms (*classic* migraine in the formerly used nomenclature). Most descriptions of a typical attack reflect an individual's composite recall of headaches in the preceding 12 months or even lifetime.[1-13] Moreover, aura symptoms often represent unusual phenomena elicited from selected migraine patients by headache specialists.

In 1986-1987, we obtained detailed information about each subject's most recent headache attack and lifetime headache history in a population-based telephone interview survey to characterize the spectrum of headache occurrence and to estimate age-specific incidence rates for migraine with and without aura.[14,15] The present analysis assessed headache attacks preceded by visual aura during the week prior to interview among the 8920 adolescents and young adults with at least one headache in the preceding year.

SUBJECTS AND METHODS

Eligible study subjects were Washington County, Maryland, residents 12 through 29 years old at interview and residing in households with telephone service (93% of county households). This community was selected because of its size (approximately 100 000) and its consistently high participation rates in previous epidemiologic investigations. The population and study methods are described in detail elsewhere.[14] In brief, Washington County is located 112 km northwest of Baltimore. Approximately half of the predominantly white (over 96%) population lives in the city of Hagerstown, while the remainder reside in small towns and rural areas.

A sampling frame of listed telephone numbers (based on a 1985 directory containing a sequential ordering of all listed telephone numbers in the county) and unlisted numbers (assigned by the telephone company to those sequential numbers missing from the directory) was created, so that approximately one half of eligible county residents aged 12 through 29 years could be contacted. Telephone interviews were conducted by trained interviewers using a standardized instrument. Informed consent was obtained directly from all participants and, additionally, from parents or guardians of minors after the procedures, risks, benefits, and methods for assuring confidentiality had been fully explained.

The response rate was 94.2%, with only 4.3% of eligible subjects refusing. The remaining eligible subjects could not be interviewed (due to mental or physical illness or language barrier) or could not be contacted (in the military, college, or otherwise not located) during the study period.

Subjects were asked about the date of occurrence and symptoms associated with their most recent headache. Two aura symptoms were assessed, both pertaining to a visual sensation:

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Distribution of 447 Subjects* With Visual Aura Headache Occurring Within 1 Week of Interview, by Age Group, Sex, and Headache Type

Visual Aura Headache Type	% of Subjects in Age Groups							
	12-17 y		18-23 y		24-29 y		All Ages	
	M (n=64)	F (n=111)	M (n=45)	F (n=85)	M (n=41)	F (n=101)	M (n=150)	F (n=297)
Aura headache without tension symptoms								
Aura only	23.4	25.3	17.8	18.8	14.6	12.9	19.4	19.2
Aura and nausea or vomiting	4.7	3.6	4.4	5.9	0	3.0	3.3	4.0
Aura and unilateral pain	18.8	27.0	31.1	18.8	24.4	7.9	24.0	18.2
Aura and nausea or vomiting and unilateral pain	1.5	9.9	2.2	3.5	2.4	4.0	2.0	6.1
Aura headache with tension symptoms								
Aura only	15.6	10.8	6.8	16.5	12.2	11.9	12.0	12.8
Aura and nausea or vomiting	4.7	4.5	2.2	4.7	4.9	8.9	4.0	6.1
Aura and unilateral pain	17.2	11.7	31.1	16.5	24.4	26.7	23.3	18.2
Aura and nausea or vomiting and unilateral pain	14.1	7.2	4.4	15.3	17.1	24.7	12.0	15.4
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

*Four hundred forty-seven subjects of 8920 Washington County, Maryland, residents participating in the headache prevalence survey, 1986-1987.

seeing "spots, lines and/or heat waves" preceding headache onset and partial loss of vision before a headache. The subject was also asked to estimate the usual length of time between the onset of the aura and the onset of the associated headache (designated the aura interval) for aura headaches experienced within the preceding 12 months. Other headache symptoms ascertained included nausea and/or vomiting accompanying a headache; headache pain on one side of the head and/or behind one eye (unilateral pain); pain in the back of the head, neck, and shoulders, and/or a feeling of a "tight band" around the head (tension headache symptoms); and forehead pain. Other topics inquired about, but not evaluated, in the present analysis included visits to a physician for headache-related problems; past 3-day exposure to six commonly implicated headache precipitators; and a history of other symptoms linked with childhood migraine (car sickness and repeated vomiting or abdominal pain).

The analysis focused on all headaches preceded by visual aura that occurred in the week before the interview. *Visual aura headaches with and without tension-type symptoms* were the two major groups considered, since earlier analyses had shown independent as well as joint occurrence of migraine and tension-type symptoms in separate headache attacks and within the same headache episode, respectively.[16] Of the four additional subtypes defined within each of the two groups (a total of eight mutually exclusive subtypes), the first subtype (aura headache without either unilateral pain or accompanying nausea and/or vomiting) was considered to be a possible episode of visual aura migraine; the fourth subtype (aura headache with both unilateral pain and nausea and/or vomiting), most likely a definite attack; and the second and third subtypes, probable attacks (Table).

Subjects were asked to report the pain intensity associated with their most recent headache attack on a scale of 1 to 10, with one being mild and 10 excruciating ("like slamming your fingers in a car door"). The interviewer also inquired about the duration of the respondent's most recent headache as well as any associated disability, defined as absence from work or school for all or part of the day. These measures of headache severity were used in comparing the two major types of visual aura headaches (with and without tension-type symptoms) with migraine headache without aura ("common" migraine) and with tension-type headache. *Migraine without aura* was defined as headache accompanied by nausea and/or vomiting and unilateral head pain or pain behind one eye, without tension-type symptoms or aura. *Simple tension-type headache* was defined as headache with pain in the back of the head, neck, or shoulders and/or a feeling of a "tight band around the head," without any of the migraine symptoms. Unfortunately, this survey was more than half completed before the new International Headache Society classification was publicly proposed.

Results for all analyses are presented separately for male and female subjects and for the age groups 12 through 17, 18 through 23, and 24 through 29 years, when numbers were sufficient. The reported usual interval between the onset of the aura symptoms and the onset of the headache was analyzed categorically (the six categories being: 1 minute or less; 2 through 15 minutes; 16 through 30 minutes; 31 through 60 minutes; 61 through 120 minutes; and greater than 120 minutes), using univariate statistics and Poisson regression modeling (log-linear model).[17] The midpoint of the interval was assigned as the aura interval score, which was modeled separately by gender and adjusted for age.

RESULTS

Attack Rates of Visual Aura Headache

Among the 8920 Washington County residents with at least one headache in the preceding 12 months (of 10 169 persons aged 12 through 29 years who were interviewed), the 1-week risk (per 100) for all visual aura headache types combined was 3.7% for male and 6.1% for female subjects. In general, the aura headache attack rate decreased with increasing age among male subjects (4.5%, 3.3%, and 3.2% for 12 through 17, 18 through 23, and 24 through 29 years old, respectively), but not among female subjects (with attack rates of 7.0%, 5.1%, and 6.2% for the same age groups). There were 4812 subjects (1783 male and 3029 female) with one or more headaches in the 7 days prior to interview, of whom 447 (8.4% of male and 9.8% of female subjects) experienced visual aura symptoms preceding their most recent headache (shown by sex, age, and aura headache subtype in the Table).

For all but the two most frequently occurring subtypes (the two types being aura headache accompanied by unilateral head pain, but not nausea and/or vomiting, with and without tension-type symptoms), the 1-week risk was one-and-a-half-

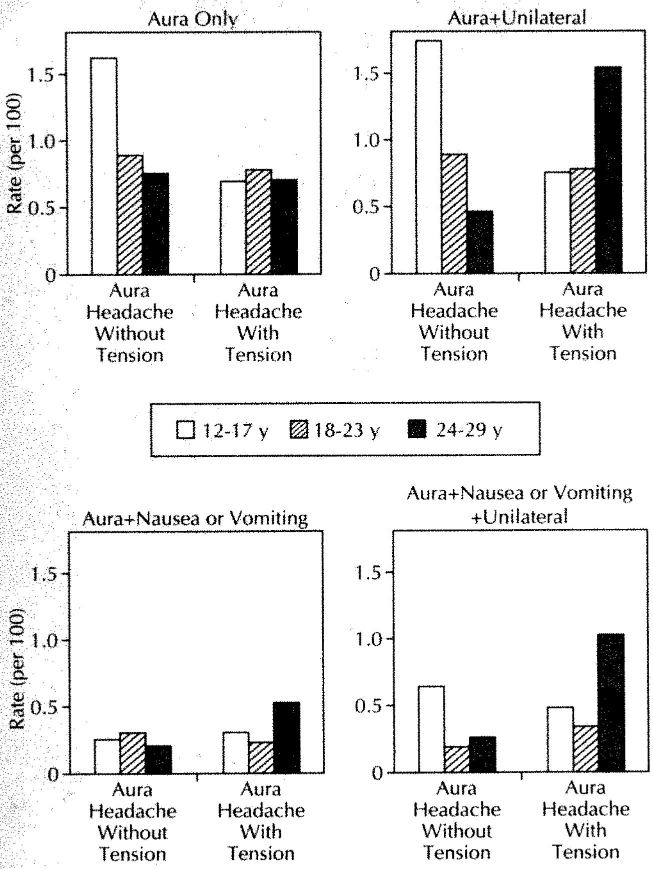

Fig 1.—*One-week risk (rate per 100) of visual aura headaches with and without tension-type symptoms by age groups and headache subtypes among 4873 Washington County, Maryland, female residents, 1986-1987.*

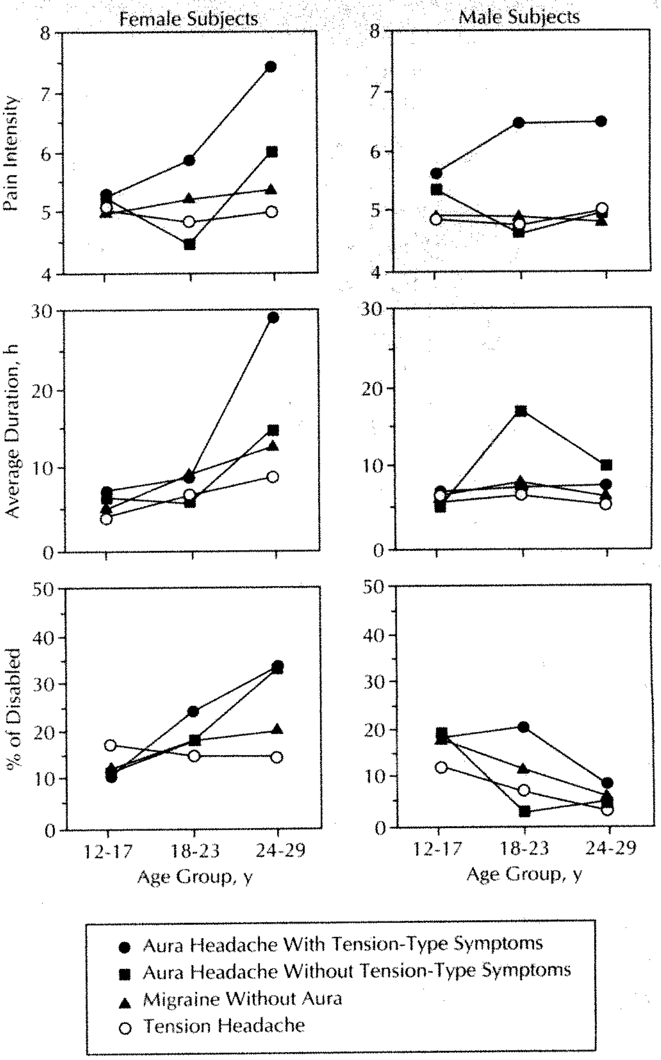

Fig 2.—*Average estimated pain, duration, and disability for headache with and without visual aura and tension symptoms, occurring within 1 week of interview, by sex and age groups, among 8920 Washington County, Maryland, residents, 1986-1987. Pain intensity was estimated using a scale of 1 to 10, with 1 indicating mild and 10 indicating excruciating.*

to fourfold higher among female than among male subjects (data not shown). Regardless of gender, visual aura headache attacks with tension symptoms were more likely to be accompanied by nausea and/or vomiting than were attacks without tension-type symptoms.

Among female subjects, the 1-week risk for most visual aura headaches without tension-type symptoms decreased with increasing age (the considerably lower risk among women 24 through 29 years old compared with that among the youngest girls was particularly striking), whereas the attack rate for visual aura headache with tension symptoms generally increased with age (being two- to threefold higher among women aged 24 through 29 years than among the youngest age group) (Fig 1). No clear age-related patterns were observed for visual aura headache attacks among male subjects, with the possible exception of those headaches with and without tension-type symptoms that were preceded by aura, but without either unilateral pain or nausea and/or vomiting (data not shown).

Headache Severity

Headache severity was assessed by reported pain intensity, headache duration, and associated disability. In general, the reported level of pain associated with visual aura headaches increased with age among female, but not among male, subjects (Fig 2). Among male and female subjects of all ages, visual aura headaches with tension symptoms were reported, on average, as being considerably more painful than the other three headache types, with somewhat smaller differences in reported pain intensity for the different headache types at younger ages. Simple tension-type headaches among male and female subjects, and migraine without aura among male subjects, were generally the least painful and showed little change in pain intensity with age. On the other hand, migraine without aura was apparently more painful for female subjects, and the pain level reported for this headache type increased with age.

Similar to the gender differences noted above for pain intensity, the reported duration of all headache types increased with age among female, but not among male, subjects (Fig 2). For female subjects, the average duration of visual aura headaches with tension symptoms ranged from 7 to 29 hours; aura headache without tension symptoms, from 6 to 15 hours; migraine without aura, from 5 to 12 hours; and simple tension headaches, from 3 to 8 hours between the youngest and oldest age groups, respectively. In contrast, male subjects in all three age groups reported similar average durations of 5 to 7 hours for aura headache with tension symptoms, migraine without aura, and simple tension headaches. No clear age-related pattern was described for visual aura headache without tension symptoms (Fig 2).

Disability associated with visual aura headaches increased with age among female subjects, but it declined with age among male subjects (Fig 2). Substantial disability was reported for both types of visual aura headaches by the oldest female subjects and the youngest male subjects. Among those reporting a visual aura headache in the previous week, 35% of women 24 through 29 years old and 19% of boys 12 through 17 years old missed all or part of a day of work or school. The reported disability from migraine without aura and from simple tension headache also decreased with increasing age among male subjects. Among female subjects, there was no apparent age trend in disability for simple tension-type headache, and only a slight to moderate trend of increasing disability with age for attacks of migraine without aura (Fig 2). Further analyses (data not shown) revealed that the substantial disability reported by women aged 24 through 29 years with visual aura headache was not due to the specific symptoms of nausea and/or vomiting, since these women did not experience these symptoms more commonly than younger women. Although men 24 through 29 years old were the least likely to be disabled by visual aura headache among all sex-age groups, when disabled, these men experienced the longest headaches (with an average duration of 30.8 hours vs 20.9 hours reported by the corresponding age group of disabled female subjects) and were more likely to experience nausea and/or vomiting than were all other subjects.

Interval Between Visual Aura Symptoms and Onset of Headache Pain

For subjects with visual aura headache, the aura interval was similar among age groups but differed by gender (Fig 3). Proportionately more female subjects in all age groups reported longer intervals than did male subjects. The median aura interval was 15 minutes in male subjects compared with 25 minutes in female subjects. Aura intervals longer than 60 minutes were reported by 12% of male subjects and 20% of female subjects.

The International Headache Society criteria for migraine with aura were first publicly reported more than halfway through the data collection and were not, therefore, incorporated in development of the questionnaire. These criteria state that the aura usually develops over 5 to 20 minutes and usually lasts less than 60 minutes. After a free interval of less than 60 minutes, the headache subsequently commences.[18]

COMMENT

In this population-based survey of headache among adolescents and young adults, several results were of interest in light of past findings. Among subjects with at least one headache during the preceding 12 months, the lower 1-week risk estimates for visual aura headache (3.7% in male and 6.1% in female subjects) compared with prevalence rates reported for other community-based studies may be due to the substantially shorter recall period used in the Washington County study. The female-to-male 1-week risk ratio of 1.6 is within the range reported in previous investigations, however. The rationale for considering visual aura headache with and without tension-type symptoms as distinct headache types was confirmed by the strikingly different age patterns for these two types among female subjects as well as the differences by sex in age patterns. Because previous community-based surveys have not assessed severity of visual aura headache either, the striking gender- and age-related differences in reported pain, duration, and associated disability represent new findings. To our knowledge, there is only one earlier clinic-based study[5] and no other population-based studies that provided detailed information on visual aura intervals for a large number of subjects.

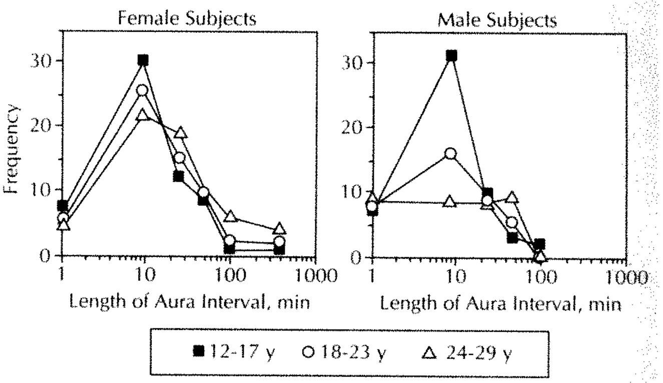

Fig 3.—*Proportion of subjects reporting aura associated with visual aura headaches, occurring within 1 week of interview, by length of interval between onset of aura symptoms and onset of headache and by sex and age groups, among 8920 Washington County, Maryland, residents, 1986-1987.*

Comparison of the Washington County findings with results of other studies is complicated by differences in populations studied, wording of questions, headache definitions, and, most important, the length of the recall period used. In general, prevalence of visual warning symptoms noted in clinic-based studies[1-6] is usually higher than rates found in community populations,[7-14] with the highest estimates based on lifetime recall. In other population-based studies,[7-14] the prevalence of visual aura headaches ranged from 3.9% to 14.1% among male subjects 15 years old or older and from 9.3% to 16.9% among female subjects. Mailed or otherwise self-administered questionnaires were most commonly used,[3,8-10] although two studies[12,13] employed in-person interviews. The majority reported separate prevalence estimates for visual aura symptoms,[3,7,8,11,14] while the remainder presented data for all aura symptoms combined.[9,12,13] Prevalence estimates for visual aura headache were lower in studies using shorter recall, with the lowest rates reported from Washington County where the shortest recall period was used.

The female preponderance for visual aura headache is consistent with the notably higher prevalence of migraine among women,[19] but restricting the denominator to those with a headache in the previous week results in a substantially smaller male-female difference (8.4% of male and 9.8% of female subjects experienced a visual aura headache). This suggests that gender is not an important factor in the probability of visual aura occurring with a specific headache. However, the differing age patterns between women and men, and the inverse age-specific trends among women for the two major types of aura headache suggest gender-related differences in etiologic factors or precipitators, as well as variation in the predominance of different precipitators at different ages among female subjects.

The age and sex variation in attack rates and patterns of the different visual aura headache subtypes suggest differences among the population subgroups and among the visual aura headache subtypes in etiologic factors or type of precipitator. In addition, the probability of attacks of different subtypes also varies by age and sex. Reasons for the sex and age differences by subtype are unknown, but possible explanations may include hormonal or other physiologic effects; differences in etiologic mechanisms; perception and/or reporting differences; and, possibly, age-related stress factor differences among female subjects. Physiologic interaction of nausea and/or vomiting with tension-type symptoms may also explain the threefold longer duration of visual aura headache with tension-type symptoms compared with the length of aura headache without tension symptoms among women 24 through 29 years old. It would be interesting to determine whether gender- and age-specific differences persist into the later decades in life.

Female subjects in Washington County also appear to experience substantial disability related to both major types of visual aura headaches. In an earlier US survey,[20] women reported higher rates of restricted activity days associated with headache than did men, but a study[21] in England did not find a similar sex difference. Neither of these previous studies specifically assessed disability associated with aura headache. The lower disability reported by Washington County men 24 through 29 years old compared with women of the same age and younger male subjects may also reflect differences in social roles or gender- and age-related expectations. For example, wage-earning men 24 through 29 years old may be more reluctant to miss work than women in the same age group and younger male subjects. On the other hand, an earlier analysis[16] of our population data also indicated that headache-related medication use increased with age among male subjects. Perhaps men 24 through 29 years old experience greater symptom relief from the medication used than do women in this age group who take the same drugs.

A possible limitation in interpreting the findings is that persons with more frequent headaches are overrepresented in the sample. In addition, the Washington County survey was not originally designed to compare standardized interviews by nonphysician interviewers with clinical evaluation by headache specialists. Absence of detailed probing and employment of nonclinician interviewers may have resulted in underascertainment of information about symptoms or overreporting of visual aura symptoms (such as mistaking blurring of vision for scotomata). In addition, aura symptoms other than visual abnormalities were not inquired about; hence, findings should not be generalized to all types of aura headaches. The visual aura headache subtype classification may not have been optimal, and it was not clinically derived. The scheme should be tested in other population-based epidemiologic studies after the method used to categorize cases is validated with a "gold standard" clinical comparison. The data represent a cross-section of headaches among a primarily white population of adolescents and young adults residing in a small city, towns, and rural areas, possibly limiting generalizability.

In summary, there appears to be a broad spectrum of visual aura headache subtypes with associated intensity, duration, and disability actually differing by age and sex or perceived differently. Future epidemiologic studies should incorporate clinical techniques such as probing and repetition of questions about a more exhaustive list of symptoms. The International Headache Society criteria (including the length of the free interval between the end of aura symptoms and the onset of headache) should also be evaluated. Thus, epidemiologists should strive to link the strengths of the survey research methodology with the best aspects of expert clinical evaluation. The results also suggest that the spectrum of visual aura headaches is broader in the general population than in the clinic setting, and that classification schemes based solely on clinic-derived experience may be incomplete.

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'Fatigue' in Patients With Multiple Sclerosis

Motor Pathway Conduction and Event-Related Potentials

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• Ten patients with a definite diagnosis of multiple sclerosis and complaints of "fatigue" were studied using (1) reaction times and event-related potentials accompanying the performance of auditory memory tasks (target detection, verbal short-term memory) and (2) motor conduction velocities of the pyramidal tract elicited by cerebral and cervical magnetic stimulation. Patients were studied when "rested" and when fatigued. Reaction times of the patients when rested were significantly delayed in the short-term memory but not the target-detection tasks when compared with normal controls. When patients were fatigued, their reaction times became significantly longer in all tasks compared with when they were rested. Event-related potentials in these tasks consist of N_1/P_2 sensory components and P_{3a} and P_{3b} cognitive components. The N_1 component latency was longer and P_{3a} and P_{3b} amplitudes were reduced in patients compared with controls. Fatigue in patients with multiple sclerosis was accompanied by a shortening of P_{3a} latency and an increase in P_{3a} and P_{3b} amplitudes compared with these measures when patients were rested. Pyramidal tract conduction velocities did not differ between rested and fatigued conditions. Thus, fatigue in patients with multiple sclerosis was associated with a slowing of performance (reaction time) on memory tasks, whereas brain potentials reflecting neural events of stimulus encoding and classification were either unchanged or paradoxically speeded up in latency in the fatigued compared with the rested conditions. We postulate that, in patients with multiple sclerosis, fatigue affects neural processes acting after stimulus evaluation but before activation of the primary motor pathways.

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Fatigue is a common experience that refers to a slowing and/or worsening of performance, usually brought about after prolonged activity.[1] While changes in muscle metabolism can follow prolonged exertion,[2] the experience of fatigue probably has multiple explanations, since it is experienced in a wide range of diseases (eg, hepatitis, cardiac failure, systemic infection) and in normal persons following effortful cognitive functions.[3] Patients with multiple sclerosis (MS) note fatigue as a major and often presenting symptom.[4,5] This experience is not restricted to motor acts but also affects cognitive activities.[6,7]

Techniques are available to quantify the function of the central pathways subserving both motor action using transcranial magnetic or electrical stimulation[8] and cognitive activity using event-related potentials recorded from surface electrodes.[9] Components of event-related potentials recorded during the performance of cognitive tasks are related to sensory processes,[10] stimulus evaluation, and stimulus classification.[11,12] Moreover, when these potentials are recorded from subjects engaged in tasks measuring particular cognitive functions, such as short-term memory, they can be related to specific activities, such as memorization,[13] maintenance of the memory trace,[14] and memory scanning.[15] Abnormalities of event-related potentials during cognitive tasks have been demonstrated in patients with MS,[16] raising the possibility that these alterations may also index altered cognitive functions accompanying fatigue. This study of patients with MS measured event-related potentials and performance (reaction time [RT] and accuracy) in tasks of auditory short-term memory (target detection to musical notes and auditory verbal short-term memory) when they were "rested" and when they were fatigued. The conduction times of the central motor pathways evoked by magnetic stimulation[8] were also measured in the rested and fatigued conditions.

SUBJECTS AND METHODS

Ten patients of both genders (two men, eight women) with a mean (±SD) age of 39.3±4.4 years (range, 29 to 43 years) participated in the study. They had a "certain" diagnosis of MS based on the criteria of at least two separate clinical episodes with neurological signs and multiple periventricular lesions on magnetic resonance imaging. Clinical details regarding the patients are contained in Table 1. We selected patients with minimal weakness or sensory loss of the upper extremities to reduce the influence of such deficits on their ability to press a response button. They were cognitively intact on clinical assessment, with Mini-Mental State[17] scores averaging 28.9 (range, 26 to 30). The extent of their fatigue on the Krupp Fatigue Severity Scale[18] averaged 5.2 (range, 2.4 to 6.8), indicating that, in general, their degree of fatigue was high. Four of the 10 patients were slightly depressed: three of them were receiving antidepressant medications (amitriptyline, trazodone). Use of these medicines was discontinued 4 days before testing. Depression can be associated with the sense of fatigue. All patients were tested on two separate occa-

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Table 1.—Patient Profiles*

Patient No./ Age, y/y From Onset/Sex	Disability Score[47]	Symptoms (Main)	MRI Lesions	Krupp Scale[18]	Medication
1/40/18/F	4	Ataxia, vision	Periventricular	4.2	Azathioprine, prednisone, amitriptyline hydrochloride
2/29/5/F	7	Ataxia, bladder, paraparesis	Periventricular, cerebellum, brain stem	2.4	Azathioprine, prednisone, alprazolam
3/40/14/F	6.5	Ataxia	Periventricular, brain stem	5.3	Baclofen
4/42/10/F	3.5	Ataxia, affect, paraparesis	Periventricular, centrum semiovale	6.8	Prednisone, azathioprine
5/39/20/F	6.5	Bladder, ataxia, numbness LEs, paraparesis	Periventricular, spinal cord, centrum semiovale, brain stem	4.4	Azathioprine, prednisone, fluoxetine hydrochloride
6/43/4/M	5	Vision, affect, weakness	Centrum semiovale, optic nerve, brain stem	6.4	Prednisone, azathioprine, trazodone hydrochloride
7/44/20/M	4.5	Ataxia, bladder, weakness	Periventricular	5.3	Azathioprine, prednisone, amitriptyline
8/38/14/F	4.5	Ataxia, memory, vertigo	Periventricular, brain stem	6.2	. . .
9/35/5/F	4.5	Vision, memory	Periventricular	5.8	. . .
10/42/5/F	4.5	Ataxia, vision, numbness	Periventricular, centrum semiovale	5.1	Amantadine hydrochloride, triazolam

*MRI indicates magnetic resonance imaging; LEs, low extremities.

sions: once in a relatively rested state and the other in a relatively fatigued state, the latter usually being late in the day. A comparison of these two states was made by grading the continuum between rested and fatigued on a scale from 0 ("without fatigue") to 10 ("the most exhausted state ever experienced"). All of the patients had a minimum difference score of 4 between the two tests. We did not counterbalance the sequence of testing, as the initial test in eight of the patients was in the rested state. We believe the role of depression in the study was minimal, since patients were tested on two occasions, usually 1 week apart, in which the extent of fatigue differed while the state of depression did not change.

Brain Potential Recordings

Subjects were seated in a sound-attenuated room with scalp electroencephalography electrodes positioned at F_z, C_z, P_z, C_3, C_4, T_5, and T_6. Electrodes on each earlobe were linked together as the reference. Eye movements were monitored from electrodes positioned above and below the right eye to assist in data analysis during the subsequent averaging procedures. The interelectrode impedances were below 2 kΩ. Brain activity was amplified with a band pass of 0.1 to 100 Hz, digitized at 200 Hz, and stored on a computer for subsequent averaging and data analysis.

Experimental Procedures

Recordings were made with the subjects wearing earphones, sitting, and fixating on a point directly ahead. They were instructed to refrain from blinking during particular portions of the tasks. Two discrimination tasks were employed that have been described in detail elsewhere,[13] and only a brief account is presented herein. The first was an auditory target-detection test, in which the subject was instructed to press an RT button "as accurately and as rapidly as possible" when the target stimulus occurred. The stimuli consisted of 300 notes, 20% of which were of a high pitch (high D) representing the target, interspersed randomly among low-pitched notes (middle C, one octave below). Stimulus duration was 50 milliseconds, intensity was 60 dB normal hearing level, and the interstimulus interval was 2 seconds.

The second task was a short-term verbal memory test in which verbal items (the digits 1 through 9) were presented in the auditory modality for memorization followed by a probe item that the subject classified (by an appropriate button press) as being (in set) or not being (out of set) a member of the preceding memory set.[19,20] Two memory set lengths were used, containing one and five items. For each memory set length, two series of 20 trials were presented, providing a total of 20 in-set and 20 out-of-set stimuli. Stimulus intensity was 60 dB normal hearing level, with the memory items presented at 1.2-second intervals. A 2-second interval separated the last memory item from the probe. Three seconds intervened before the start of the next trial.

Event-Related Potentials

Averaged brain potentials were made to the probes in the short-term memory task and to the targets in the target detection task that had a correct response without an eye blink in the 1-second period surrounding the stimuli. The averages were 1 second in length for targets and 1.28 seconds in length for probes, and both included a 120-millisecond prestimulus baseline. The latencies and amplitudes of the averaged event-related potentials recorded at the P_z electrode to the targets were measured at the peaks close to 100 (N_1), 200 (P_2), 280 (N_2), and 300 milliseconds (P_{3b}). In the short-term memory tasks, the potentials to the probes at the P_z electrode were measured at the peaks close to 150 (N_1), 250 (P_2), 300 (N_2), and 450 milliseconds (P_{3b}), all slightly delayed compared with the peaks of the averaged potentials to the notes used in the target detection task. The P_3 components of the target and probe evoked potentials also have an early peak, P_{3a}, most prominent in the frontal lead from which peak measures were made. The P_{3b} components were also measured using an average amplitude in a 500-millisecond time window fixed from 450 to 950 milliseconds for the short-term memory task and in a 200-millisecond window for the target-detection task with the midposition adjusted for each subject to coincide with the peak of P_{3b}.

Motor Evoked Potentials

A magnetic stimulator coil (Cadwell MES-10, Cadwell Lab Inc, Kennewick, Wash; coil diameter, 9.5 cm) was used to activate the motor cortex and cervical roots. Recording electrodes were placed on the skin overlying the opponens pollicis muscle con-

Table 2.—Behavioral Measures*

	Tasks		
	TD	STM, 1 Item	STM, 5 Items
		Reaction Time, ms	
Controls	368±110	562±93	764±128
Patients			
Rested	477±140	899±146†	1358±243†
Fatigued	556±178‡	1042±266‡	1425±257‡
		Accuracy, %	
Controls	99.9±0.1	99.7±0.3	99.7±0.3
Patients			
Rested	99.9±0.1	98.2±0.5	92.7±1.6†
Fatigued	99.8±0.2	98.5±0.5	90.7±2.1

*TD indicates target detection; STM, short-term memory.
†$P<.05$, patients rested vs controls.
‡$P<.05$, patients fatigued vs patients rested.

tralateral to the cortex and ipsilateral to the root being stimulated. The magnetic stimulus duration was 0.07 milliseconds, and its intensity was gradually increased until a reproducible electromyographic potential was obtained both in a relaxed state and with minimal contraction of the opponens pollicis. The difference in latency between the electromyographic potential onset to cortical and to nerve root stimulation represents the conduction time of the central motor pathway.

Data Analysis

The results from a group of 10 young normal subjects (average age, 29 years; range, 18 to 45 years) previously tested with the same paradigms[13] were included in these analyses. The controls were approximately 10 years younger than the patients. While it is ideal to have no difference, studies of RTs using larger numbers of subjects over a wide age range are essentially no different across the decades for 20- to 30- vs the 30- to 40-year-olds.[21,22] Event-related potential amplitudes can decrease with age, but the differences only become significant with 30- to 40-year age disparities.[23] Measures of RT, accuracy, and the amplitudes and latencies of event-related potentials were tested for significance using analysis of variance for the factors of the patients' state (rested, fatigued), task type (short-term memory, one item; short-term memory, five items; target detection), and subject type (patients when rested, controls). The data for the in-set and out-of-set probes in the short-term memory tasks were combined since a separate analysis (analysis of variance) of the results from the short-term memory tasks showed no significant differences as a function of probe type. Significance level was set at $P<.05$ after adjusting with the Greehouse-Geisser correction factor. Significance of interactions in the analysis was evaluated using the Neumann-Keuls correction.

RESULTS

Behavior

Across all subjects, accuracy was almost perfect (>99%) in the target-detection and the one-item short-term memory tasks but decreased significantly ($P<.001$) from 96% in the five-item short-term memory task. The reduction in accuracy on the five-item task was due to the patients with MS, whose performance decreased to 92.8% correct when rested compared with the controls' accuracy of >99% ($P<.001$; Table 2, Fig 1). The patients' performance decreased to 90.8% when they were fatigued, but the change was not significantly different from their performance when they were rested.

Reaction times (Table 2) were significantly different ($P<.001$) as a function of task, being longest with the five-item short-term memory task (1392 milliseconds), intermediate in the one-item task (971 milliseconds), and shortest in the target-detection task (517 milliseconds) across all subjects (rested patients and controls). Reaction times were significantly longer ($P<.01$) in patients with MS when rested compared with controls (Fig 1) for the short-term memory tasks (a difference of 337 milliseconds for one-item and 594 milliseconds for five-item task), but the difference (110 milliseconds) for the target-detection task did not achieve significance. For the patients, RTs increased significantly ($P<.05$) between the rested and fatigued states in all tasks, ranging on the average between 80 and 150 milliseconds. Thus, patients with MS when rested have significantly longer RTs as a group

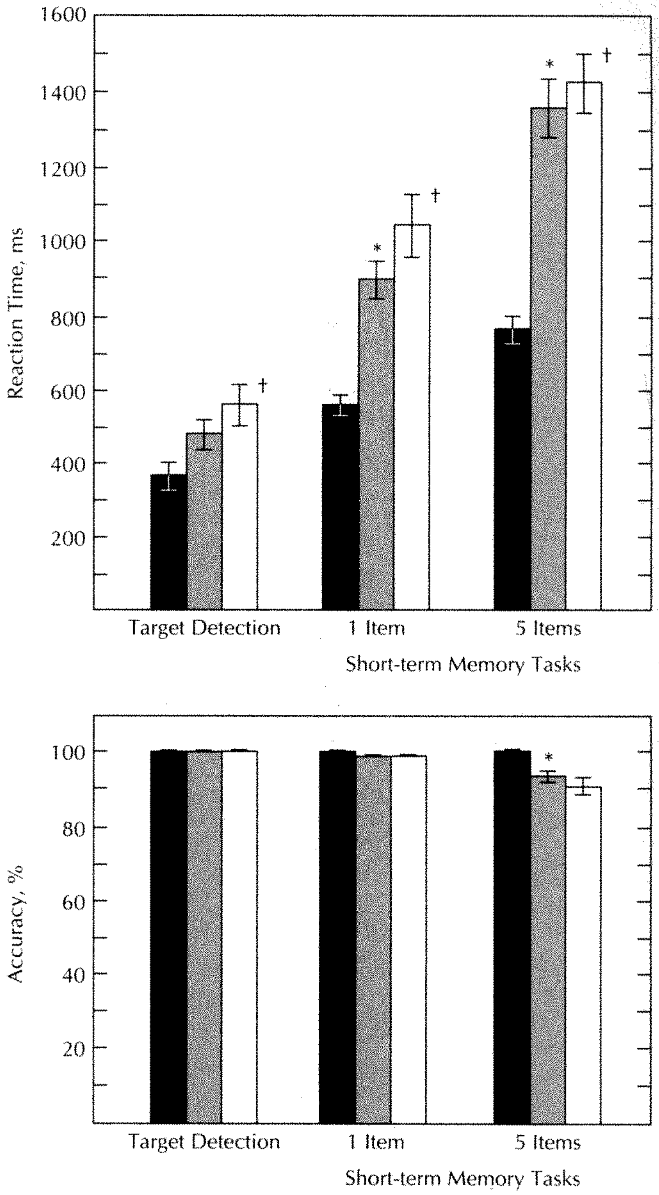

Fig 1.—*Bar graph of reaction times (RTs) and accuracy for controls (closed bars) and patients with multiple sclerosis (MS), rested (shaded bars) and fatigued (open bars), for the target-detection and short-term memory tasks. Asterisk indicates* $P<.05$ *for controls vs patients with MS when rested; dagger,* $P<.05$*, patients rested vs patients fatigued. Note the striking effect of task on RTs of the patients and the consistent lengthening of RT in patients when fatigued compared with when rested.*

compared with controls, and when patients with MS become fatigued, their RTs become even further delayed. An analysis of RT for each patient with MS showed that eight of 10 had longer RTs when fatigued compared with the rested condition for the short-term memory tasks and seven of 10 for the target-detection task.

In short-term memory tasks, RTs increase in a linear manner with memory load. The slope of this function, expressed in milliseconds per item, has been proposed as a measure of the time required to scan the contents of the short-term store before a response can be made.[19] In the control subjects of this study, scanning times averaged 50.5 milliseconds per item for auditory verbal material, while in the patients with MS scanning times increased significantly ($P<.05$), more than twofold, to 115 milliseconds per item without any further significant changes with fatigue (Fig 1).

Event-Related Potentials

Latency.—The evoked potentials to the stimuli used in these tasks consist of the initial short-duration negative/positive sensory complex (the N_1/P_2) between approximately 100 and 300 milliseconds, a subsequent negative wave, the N_2 (200 to 300 milliseconds), followed by a cognitive long-duration (500 milliseconds) positive component beginning at about 350 milliseconds. The latency of all the peaks differed significantly ($P<.001$) between tasks, being longer in the short-term memory tasks compared with the target-detection task (Table 3). The magnitude of the difference was approximately 50 milliseconds for N_1, P_2, and N_2, most likely reflecting differences in the rise times of the acoustic stimuli in the tasks: the digits used in the short-term memory tasks have an acoustic envelope with gradual rise times (up to 50 milliseconds), while the the notes used in target-detection had relatively fast rise times (5 milliseconds). Onishi and Davis[24] have shown the latency of the N_1/P_2 components to increase when rise times exceed 30 milliseconds. The latency difference for the P_3 components varied from 70 milliseconds for the frontal P_{3a} component to as much as 330 milliseconds for the parietal P_{3b} component. The magnitudes of these differences are unlikely to be due to the physical nature of the stimuli but, rather, to differences in the cognitive demands of the two tasks (target detection vs verbal short-term memory), as is evident in RT differences.

The latency of the event-related potentials differed significantly ($P<.05$) between controls and patients for only the N_1 component in all tasks, being approximately 15 milliseconds longer in the patients. A significant difference was noted in the latency of the P_{3a} component for all tasks as a function of the patients' state, ie, rested vs fatigued: P_{3a} was of shorter latency when the patients were fatigued compared with when they were rested, with the difference ranging from 15 milliseconds for target-detection to 29 milliseconds for short-term memory tasks. No other differences in peak latencies were defined.

The interval between N_1 and P_{3a} is a measure of the temporal pace of brain events accompanying the processing of acoustic stimuli reflecting the period between sensory processes (N_1) and cognitive evaluation (P_{3a}). This interval was approximately 250 milliseconds and did not differ significantly between tasks or between controls and patients with MS. The N_1 to P_{3a} interval in patients with MS was approximately 20 milliseconds less when they were fatigued than when rested in the short-term memory tasks, but the difference did not reach statistical significance.

In normal subjects, the latency of P_{3b} increases with memory load in a linear manner, with a slope of approximately 25 milliseconds per item,[13,25] approximately half that of the slope for RT. In the patients of this study, P_{3b} latency did not change significantly between the one- and five-item memory loads in distinction to the prolonged scanning rates apparent from RT measures.

Amplitude.—Only the amplitudes of the P_{3a} and P_{3b} components were significantly affected by the experimental variables: P_{3a} and P_{3b} significantly ($P<.001$) differed according to task, being larger for target-detection than for short-term memory tasks (Table 3). The patients had significantly ($P<.05$) lower amplitudes than the controls for P_{3b} (peak measure in the one-item short-term memory task; average amplitude in both the one- and five-item tasks). These differences are apparent in the grand averages plotted in Fig 2. Inspection of the individual averages in the short-term memory tasks also reveals that the sustained positivity, P_{3b}, characteristic of the normal subjects was of negative rather than of positive polarity in four of the 10 patients. The amplitude of the frontal P_{3a} component differed significantly as a function of the patients' state (rested vs fatigued) for all tasks, with P_{3a} amplitudes being larger when patients were fatigued than rested. The grand averages of the potentials recorded from F_z in the patients with MS when rested and fatigued are contained in Fig 3.

Motor Evoked Potentials

The motor potentials evoked by magnetic stimulation were tested in the rested and fatigued conditions in nine of the patients. In three of these patients, motor evoked potentials from stimulation of the motor cortex could only be obtained when the opponens pollicis was voluntarily contracted to a slight degree (facilitation). The central conduction times to the cervical cord were abnormal in three patients (>12.5 milliseconds without facilitation and >11 milliseconds with facilitation). The group average (Table 4) of 13.0±1.8 milliseconds without facilitation and 10.3±3.6 milliseconds with facilitation is slightly greater than the normal values from our laboratory (9.5±1.2 and 8.0±1.2 milliseconds, respectively). No significant difference was noted in central motor conduction times in the patients when rested and when fatigued. In addition, no significant correlation was found between central motor conduction times and RTs in each of the tasks.

COMMENT

The results of this study of a group of patients with MS show that performance and brain potentials were affected in different ways by fatigue. Reaction times were prolonged in a simple auditory discrimination task (distinguishing an infrequent high note, the target, randomly occurring during a sequence of frequent low notes requiring a go/no-go response) and in a complex auditory verbal short-term memory task (distinguishing whether a probe item was or was not a member of the preceding memory list, requiring a two-alternative forced-choice response). In contrast, the event-related potentials to the target or the probe were no different between the rested and fatigued conditions except for the cognitive component, P_{3a}. The latency of this component paradoxically

Table 3.—Evoked Potentials*

Peaks	Subjects	Tasks		
		TD	**STM, 1 Item**	**STM, 5 Items**
		Latency, ms		
N_1	Controls	102±13	157±18	150±13
	Patients			
	Rested	115±10†	165±24†	168±15†
	Fatigued	113±17	159±10	163±17
P_2	Controls	174±12	235±18	225±33
	Patients			
	Rested	185±17	242±29	239±21
	Fatigued	182±14	248±17	245±22
N_2	Controls	224±17	287±13	302±30
	Patients			
	Rested	231±18	310±37	327±50
	Fatigued	229±16	313±33	328±47
P_{3a}	Controls	333±18	403±30	407±29
	Patients			
	Rested	356±34	420±31	448±62
	Fatigued	340±39‡	396±27‡	419±62‡
P_{3b}	Controls	351±33	579±101	686±93
	Patients			
	Rested	359±34	670±51	686±38
	Fatigued	355±35	663±92	683±78
$P_{3a}-N_1$	Controls	231±25	246±39	257±34
	Patients			
	Rested	241±37	254±39	279±64
	Fatigued	226±37	237±29	256±66
		Amplitude, v		
N_1	Controls	−3.4±2.6	−4.4±2.4	−4.9±2.5
	Patients			
	Rested	−4.2±1.9	−4.4±2.8	−4.3±3.0
	Fatigued	−3.8±2.9	−4.2±2.5	−4.7±2.5
P_2	Controls	2.1±2.2	1.6±2.5	0.9±2.2
	Patients			
	Rested	3.4±2.8	1.6±2.8	2.5±2.3
	Fatigued	3.4±3.4	3.2±3.2	2.1±1.8
N_2	Controls	−1.3±2.4	−0.6±2.4	−2.8±1.8
	Patients			
	Rested	−0.7±3.2	−2.5±2.6	−2.8±2.1
	Fatigued	−0.9±4.1	−0.4±2.3	−2.0±1.6
P_{3a}	Controls	3.9±4.1	3.5±2.4	1.1±2.0
	Patients			
	Rested	5.8±3.6	3.6±2.9	1.1±2.5
	Fatigued	7.2±2.5‡	5.3±2.7‡	2.1±2.0‡
P_{3b}	Controls	14.2±5.1	11.2±3.5	10.0±4.5
	Patients			
	Rested	12.6±4.6	3.8±4.0†	5.2±5.0
	Fatigued	12.1±4.4	5.7±2.6	6.1±2.5
Average amplitude, P_{3b}	Controls	9.6±3.9	6.7±2.7	7.3±3.6
	Patients			
	Rested	8.1±3.7	1.4±3.6†	2.2±3.9†
	Fatigued	8.1±3.4	2.7±2.3	2.8±2.3

*TD indicates target detection; STM, short-term memory.
†$P<.05$, patients rested vs controls.
‡$P<.05$, patients fatigued vs patients rested.

decreased and its amplitude increased with fatigue in all of the tasks. Finally, the central conduction times of the pyramidal motor pathways were no different between the fatigued and rested states. Thus, fatigue in patients with MS is associated with a prolongation of RT without change in pyramidal tract conduction times.[8] Brain potentials reflecting neural events of sensory processes and stimulus evaluation[12] were generally no different between rested and fatigued states except for a particular frontal component, P3a, which was paradoxically shortened in latency and increased in amplitude with fatigue.

The P_3 components of event-related potentials can be divided into an early component, P_{3a}, maximal frontally, and a later component, P_{3b}, maximal parietally,[26,27] reflecting neural events underlying stimulus evaluation. The amplitudes of these components are dependent on factors

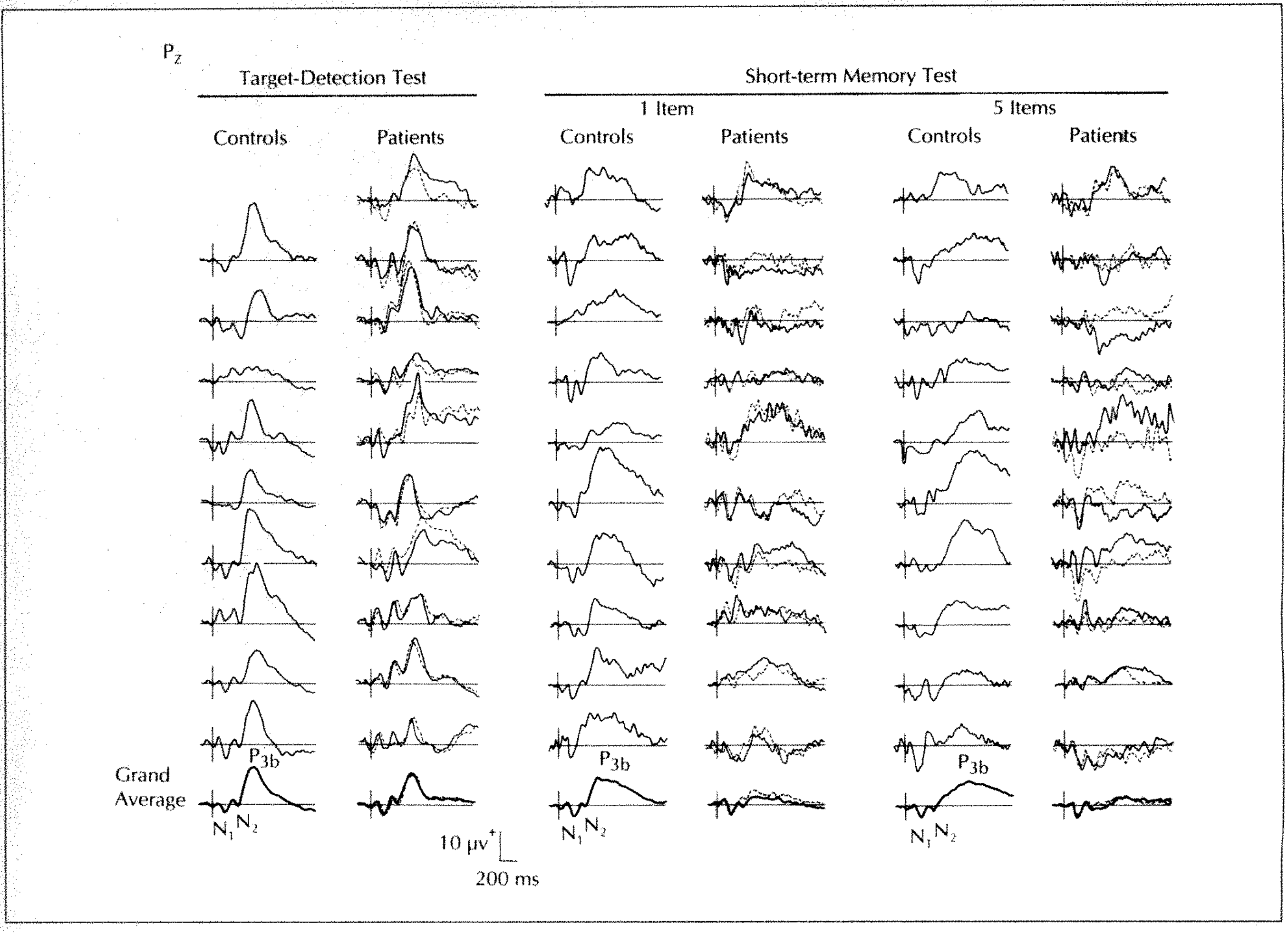

Fig 2.—*Individual and grand average evoked potentials recorded from the P_z electrode in target detection and short-term memory tasks for controls and for patients with multiple sclerosis (MS), rested (solid tracing) and fatigued (broken tracing). Note that the positive potential, P_{3b}, is smaller in amplitude in patients with MS than in controls in the short-term memory tasks but not in the target-detection task. There is no consistent difference across all tasks between the rested and fatigued conditions. Measures of latency and amplitude of the various peaks are given in Tables 2 and 3.*

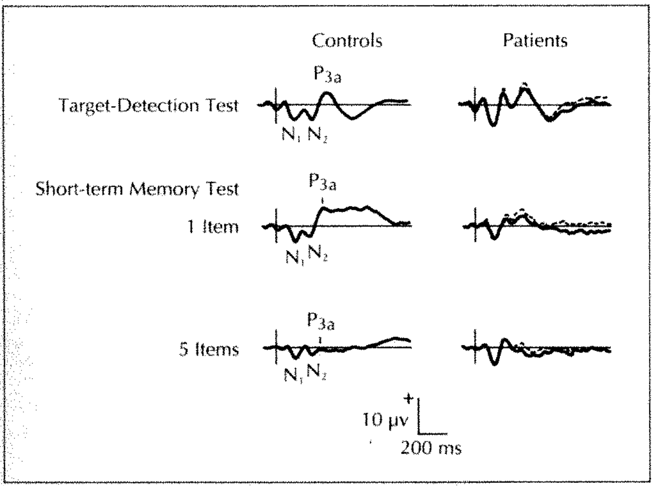

Fig 3.—*Grand-averaged evoked potentials recorded from the F_z electrode in controls and in patients with multiple sclerosis when rested (solid tracing) and fatigued (broken tracing). Note the increase in amplitude of the P_{3a} positive component in all three tasks when patients were fatigued compared with rested.*

Table 4.—Central Motor Pathway Conduction Times (ms), Cortex to Cervical Cord

	Patients		
	Rested	**Fatigued**	**Normal Controls**
Relaxed	13.0±1.8	13.6±3.9	9.5±1.2
Facilitated	10.3±3.6	11.6±4.7	8.0±1.2

of stimulus probability and task difficulty.[28] The amplitudes of the two subcomponents of P_3 behave differently, depending on the relationship between the stimulus and the subject's instructions. A P_{3a} can appear in response to a novel stimulus in the absence of any instruction to the subject to process that stimulus,[29] suggesting that it is associated with neural events subserving arousal. In contrast, the appearance of a P_{3b} requires the subject to process and respond to the stimulus.[30] The finding, in this study, that P_{3a} amplitude is increased and its latency shortened in patients with MS when fatigued compared with the rested state may reflect that fatigue involves neural systems regulating arousal. The failure to detect changes in the P_{3b} component indicates that neural systems subserving stimulus classification appear to be relatively unaffected by fatigue.

Fatigue in patients with MS is accompanied by prolonged RTs without changes in P_{3b}, indicative that neural processes intervening between stimulus evaluation and the initiation of motor events are affected. This would encompass the period between the P_{3b} component, reflecting stimulus evaluation, and the period of activation of pyramidal tract neurons subserving motor systems used in the button press. In normal subjects engaged in the one-item memory-scanning task, we estimate this period to be approximately 160 milliseconds in duration, beginning with the onset of the P_3 component, which is at about 300 milliseconds after the probe's presentation, and ending just before the activation of pyramidal tract neurons used in the button press response (at about 460 milliseconds, 80 milliseconds before the actual RT of 540 milliseconds).[31,32] For the target detection task, the period intervening between the onset of the P_3 component, at approximately 250 milliseconds, and the activation of pyramidal tract neurons, at approximately 290 milliseconds, is only 40 milliseconds in duration. Using these same methods for the data from patients with MS, the period intervening between stimulus evaluation and motor pathway activation in the one-item memory-scanning task is threefold longer than in normal subjects, being almost 450 milliseconds in duration. When these patients are fatigued, the period increases even further, to 900 milliseconds. For the target detection task, the values are 150 milliseconds when rested and 225 milliseconds when fatigued. Thus, for patients with MS, the time intervening between brain events subserving stimulus evaluation and those involved in the initiation of motor responses is prolonged for simple and complex auditory discriminations, and these periods become further prolonged with fatigue.

There are several mechanisms by which fatigue could impair performance on the tasks used in this study. First, fatigue could affect attention, leading to impaired performance. We do not think this possibility is likely, since only RT and not accuracy changed between the rested and fatigued conditions.

A second possibility is that alterations in stimulus evaluation could lead to impaired performance, particularly when the subject is fatigued. Brain potentials accompanying the stimuli being evaluated differed considerably from those of normal subjects when rested.[16] It may be that performance based on altered neural processing of sensory information would be subject to additional impairment when subjects become fatigued. For example, for normal subjects performing discrimination tasks, P_3 latencies and RTs are prolonged when sensory stimuli are degraded compared with these measures when the sensory stimuli are clear.[33]

A third possibility is that core temperature is raised in patients with MS when fatigued, leading to alterations of nerve conductions in demyelinated fibers.[34] While we did not measure our patients' temperature, we do not think this possibility likely since pyramidal tract conduction velocities did not differ between the rested and fatigued states.

A fourth consideration is that a circulating neurohumoral factor is present in the brains of patients with MS that affects neural functions, leading to fatigue. An example of such a factor is interleukin 2, which has been discussed as participating in the symptoms of neural dysfunction in certain immune states.[35] Such a factor might act to "disconnect" neural systems subserving stimulus evaluation from response systems.[36] The sites of many of the lesions of MS are in the periventricular and subcortical white matter, well disposed to affect pathways interconnecting sensory, cognitive, and motor cortices involved in auditory discrimination tasks.[37-40] Changes in the synchrony of activity or the speed of conduction between these sites could account for the findings of delayed RTs in patients with MS accompanying fatigue.

The "readiness" or premovement potential reflects neural events underlying the initiation of motor responses.[41,42] In normal subjects, when a particular movement is fatigued with repetition, premovement potentials become larger, presumably reflecting increased central "effort" to accomplish the same motor task.[43] The analysis of such premovement potentials in patients with MS would appear to be an appropriate direction for investigation.

Fatigue is a frequent concomitant of a variety of illness, such as systemic viral infections,[44] depression,[1,45] or strokes.[46] The present study in patients with MS has provided measures of fatigue that could be examined in other disorders characterized by easy fatigability. For instance, in a recent study in patients with fatigue accompanying myalgic encephalomyelitis,[47] RT and P_3 components of event-related potentials were abnormally delayed compared with controls, findings that differed from this study of patients with MS. Finally, the experience of fatigue in normal subjects could also be examined to define if alterations in RTs or event-related potentials are present. In a preliminary study of two normal subjects, fatigued after sleep deprivation or overwork, RTs and brain potentials were unchanged.

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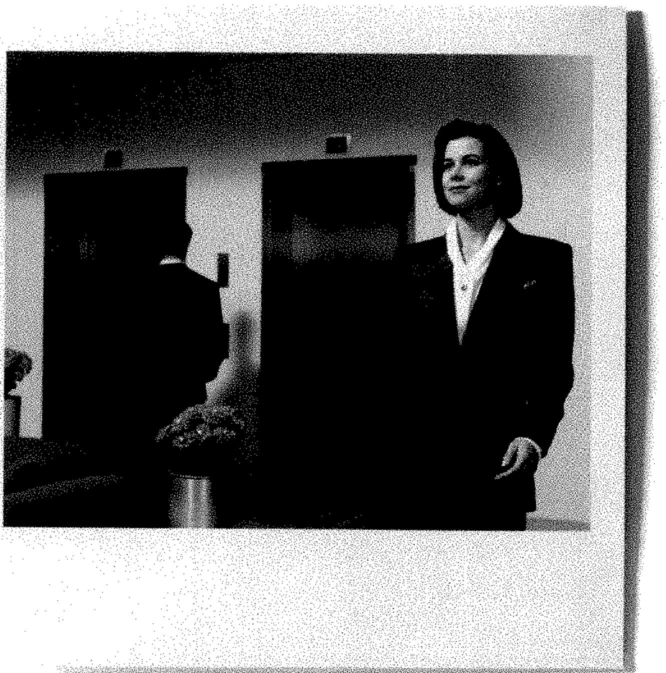

A proven combination for the symptom complex of tension headache, including the pain-relieving potency of codeine.

FIORINAL® WITH CODEINE CAPSULES CIII

Please see brief summary of prescribing information on following page.

(Each capsule contains: codeine phosphate 30 mg; [Warning: May be habit-forming]; butalbital 50 mg; [Warning: May be habit-forming]; caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

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BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE CIII CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming], butalbital USP, 50 mg [warning: may be habit forming], caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiorinal® with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	**Fiorinal®/Codeine (N = 382)**	**Placebo (N = 377)**
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caused by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® with Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorinal® with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overdosage is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion, and coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus; hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restlessness, tremor, and delirium, tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® with Codeine. However, because strategies for the management of an overdose continually evolve, consultation with a regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g

Aspirin: toxic blood level greater than 30 mg/100 mL, lethal dose 10-30 g (adult)

Caffeine: toxic dose greater than 1.0 g; lethal dose unknown

Codeine: lethal dose 0.5-1.0 g (adult)

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[NOVEMBER 1, 1990 FWC-Z26]

Failure to Activate the Left Temporoparietal Cortex in Dyslexia

An Oxygen 15 Positron Emission Tomographic Study

Judith M. Rumsey, PhD; Paul Andreason, MD, MS; Alan J. Zametkin, MD; Tracy Aquino, MA; A. Catherine King;
Susan D. Hamburger, MS; Anita Pikus, MA; Judith L. Rapoport, MD; Robert M. Cohen, MD, PhD

• To test the hypothesis of left temporoparietal dysfunction in dyslexia, suggested by neuropsychological and neuropathologic data, cerebral blood flow was measured with positron emission tomography in 14 right-handed men with severe developmental dyslexia (mean [SD] age, 27 [5] years; median reading level, fifth grade) and 14 matched controls at rest and during an auditory phonologic task (rhyme detection) and an auditory attention task involving the detection of target tones. As expected, normal readers activated left temporoparietal cortex during rhyme detection but not during the nonphonologic attentional task. Dyslexic men failed to activate those left temporoparietal regions activated in controls during rhyme detection but did not differ from controls in these regions during rest or attentional testing. Thus, the expected left temporoparietal dysfunction was demonstrated only when specific probes for these regions were employed.

(*Arch Neurol.* 1992;49:527-534)

Developmental reading disorder, or "dyslexia," is a common disorder, affecting 2% to 8% of the school-age population in the United States.[1,2] When severe, dyslexia persists into adulthood.[3,4] While previously believed to affect about five times more males than females, new epidemiologic data and genetic studies not biased by clinic and school referrals suggest a male to female ratio of 2:1 or less.[2,5]

Neuropsychological studies have identified subtle language-based deficits and specific phonologic deficits (ie, problems in processing speech sounds), implicating left hemisphere involvement, in a majority of cases.[6] Genetic studies suggest that deficits in phonologic coding, believed to be dependent on the left angular/supramarginal cortex, are inherited and constitute a core deficit or common neuropsychological pathway to dyslexia.[7] Postmortem studies of four male dyslexic brains[8] found neuronal ectopias and dysplasias affecting predominantly left perisylvian language regions. Thus, neuropsychological, genetic, and limited neuropathologic data converge to suggest a hypothesis of left temporoparietal dysfunction as a basis for dyslexia.

Phonologic awareness as operationalized by rhyme detection is an early (preschool) predictor of the ability to learn to read.[9] Dyslexic adults, even those with good outcomes, continue to show deficits specifically in the phonologic aspects of reading, as manifested in poor nonword reading and poor spelling.[10] Thus, rhyme detection is expected to constitute a relatively easy phonologic task, and nonword reading and spelling, more difficult and more sensitive tests of phonologic deficits in adults.

Using positron emission tomography (PET) of the brain with oxygen 15–labeled water as a tracer to measure cerebral blood flow, we studied healthy men with persistent, severe developmental dyslexia during rest and during the performance of an auditory rhyme detection task expected to activate the left temporoparietal cortex in matched controls. An easy phonologic task was selected so that physiologic differences could not be attributed to an inability of the dyslexic subjects to adequately perform the task. Dyslexia was defined by history and by current test evidence of deficient "decoding" skill, or poor word recognition and reading accuracy (as opposed to comprehension), relative to both general and verbal intelligence. The reading deficits could not be attributed to low IQ, disorders of spoken language, inadequate educational opportunity or sensory deficits, trauma (eg, early head injury), or neurologic disease.

We hypothesized (1) that rhyme detection would activate left temporoparietal regions near the angular gyrus in controls and (2) that dyslexic men would fail to show normal patterns of activation in these same regions during phonologic processing. Both hypotheses were confirmed. Dyslexic subjects, failed to activate left posterior language regions (that were activated in controls) during

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Table 1.—Sample Description

	Mean (SD)	
	Controls (n = 14)	Dyslexics (n = 14)
Age, y	26 (5)	27 (5)
% Right-handed (Physical and Neurological Examination for Subtle Signs)	99 (2)	96 (7)
Education, highest grade completed	13 (1)	14 (2)
Socioeconomic status (Hollingshead Scale)*		
Father	79 (32)	55 (28)†
Mother	72 (24)	74 (20)
Subject	74 (12)	74 (16)
Wechsler Adult Intelligence Scale–Revised IQS (mean = 100, SD = 15)		
Full Scale	111 (9)	105 (9)
Verbal	110 (9)	102 (9)†
Performance	110 (10)	110 (10)
Academic achievement		
Wide Range Achievement Test–Revised (WRAT-R) (mean = 100, SD = 15)		
Reading (single words)	109 (7)	81 (15)‡
Spelling	106 (8)	67 (10)‡
Math	103 (14)	86 (11)§
Gray Oral Reading Test		
Grade equivalent	12 (0)	5 (3)‡
Finucci deviation quotients‖		
Reading (Gray)	1 (1)	−4 (2)‡
Spelling (WRAT-R)	1 (1)	−3 (1)‡
Goldman-Fristoe-Woodcock Reading of Symbols (nonwords) (n = 8) (mean = 50, SD = 10)	51 (6)	39 (5)‡

*Scores of 19 to 31 indicate upper upper class; 32 to 55, lower upper class; 56 to 86, upper middle class; and 87 to 115, lower middle class, based on education and occupation.

†$P<0.5$.

‡$P<.0001$.

§$P<.01$.

‖Deviations (in SE) from scores predicted from subjects' IQ scores and education.

rhyme detection, thus supporting the hypothesis of left posterior temporoparietal dysfunction. These effects were specific to the phonologic, rhyme detection task, as the tone detection task failed to activate these regions in controls, and failed to reveal group differences in blood flow in these regions.

SUBJECTS AND METHODS

Informed Consent

This study was reviewed and approved by the Human Subjects Protection Committee of the National Institute of Mental Health and the Radiation Safety Committee of the National Institutes of Health, both in Bethesda, Md. Following a full explanation of the procedures, informed consent was obtained from all subjects before the study began.

Sample

Fourteen right-handed men (age range, 20 to 41 years; mean [SD] age, 27 [5] years) with severe developmental dyslexia and 14 matched controls (described in Table 1) were studied at rest and during the performance of a rhyme detection task. To provide a contrast condition for the activation seen in left temporoparietal regions, 16 controls (11 of the above-described controls and five additional controls) and 12 dyslexic subjects were studied during the performance of a Continuous Performance Test, an auditory attentional task involving tones.

In addition to histories of reading disability, the dyslexic subjects had Wechsler Adult Intelligence Scale–Revised (WAIS-R) Verbal *or* Performance IQs of at least 89 and met *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*[1] criteria for developmental reading disorder and Finucci[11] criteria for severe dyslexia in adults. All wrote with and responded to at least 10 (83%) of 12 handedness items from the Physical and Neurological Examination for Subtle Signs (PANESS)[12] with the right hand. Poor educational opportunities, non-English or bilingual backgrounds, neurologic disease or seizures, head injury, severe psychiatric disorder, chronic substance abuse, and uncorrected visual or hearing impairment were exclusionary.

All the dyslexic subjects had had some special educational services, ranging from minimal part-time help (eg, tutoring and resource help) to 7 years of full-time special education. Only one dyslexic man had been diagnosed as hyperactive during childhood; none had been diagnosed with a developmental language disorder, showed spoken language impairment, or reported a history of language delay (eg, failure to talk in two-word sentences by 3 years of age).

Controls were matched to the patients by age, sex, handedness, educational level, and Full Scale IQ. Controls were free of developmental disorders or a history of such and showed no significant deficits on reading or spelling tests. The same exclusionary criteria were applied to controls as to the dyslexic subjects.

Evaluations included a semistructured intake interview, a structured psychiatric interview (Schedule for Affective Disorders and Schizophrenia–Lifetime version),[13] psychometric testing (WAIS-R, Gray Oral Reading Test [Form C], Wide Range Achievement Test–Revised [WRAT-R], Goldman-Fristoe-Woodcock [GFW] Reading of Symbols [nonwords]), 12 handedness items involving pantomimed responses to verbal commands from the PANESS,[12] a general physical examination, a physical neurologic examination, and audiologic assessment. All subjects had normal, bilaterally symmetrical hearing for speech and were free of medications that had central nervous system effects for 30 days before scanning.

Positron Emission Tomography

Before scanning, subjects were trained with regard to the tasks to ensure adequate understanding and performance. A catheter was placed in the radial artery of the right arm and an antecubital vein of the left arm. In a few cases in which it was not possible to place an arterial line in the right arm, the sides of these lines were reversed. Subjects were placed in a supine position on the scanner table and fitted with a custom-molded thermoplastic head-holding device that was fixed to the scanner table with a quick-release clamp. Subjects' eyes were closed and patched, and insert earphones (Tubephone ER-3A, Etymotic Research, Elk Grove Village, Ill) were placed in the subjects' ear canals. A button press was placed in the right hand.

Scanning was performed with a Scanditronix positron emission tomograph scanner (PC1024-7B, Scanditronix, Uppsala, Sweden). Seven slices with an in-plane resolution of 5.2 mm and an axial resolution of 10 mm (full width at half maximum) were obtained simultaneously.

A transmission scan, one "mock" resting scan, and six emission scans were performed. Transmission scan employed a rotating germanium 68/gadolinium pin source or an ^{18}F ring source of 511-keV photons placed into the tomograph and provided a measured attenuation correction for each subject. Saline solution, rather than a tracer, was injected during the first "mock" resting scan, which followed transmission scan, to habituate subjects to the scan procedure without exposing them to unnecessary radiation. Subjects were unaware that this first injection did not contain tracer. The emission scans that followed each in-

involved an injection of 1.11 GBq of ^{15}O-labeled water in a 10-mL total volume of saline solution. Data collection for each scan continued for 4.5 minutes after the injection.

Following each injection of tracer, a time-activity curve was generated by sampling blood from the radial artery and measuring its volume and radioactivity. Blood gas levels were also determined. Regional cerebral blood flow values were calculated from the count data with use of the method described by Alpert et al.[14]

The resting scan was obtained as the third emission scan. Subjects were instructed to lie still, to keep their eyes closed, and to remain awake.

The rhyme detection scan began 1 minute before the injection and continued throughout the scan. Position varied but was the same for each group. Subjects listened to pairs of one- to three-syllable words (50% of the pairs rhymed) presented binaurally at a rate of 16 per minute at an average intensity of 67 dB through the insert earphones (eyes still closed and patched). Subjects were instructed to press the button if the paired words rhymed. This easy task was used to ensure adequate performance by the dyslexics and to minimize group differences in performance.

The Continuous Performance Test also began 1 minute before the injection and involved listening to a series of 500-Hz tones with intensities of 67, 75, and 86 dB through insert earphones (with the eyes closed and patched). The tones were 1 second in duration with a 2-second interstimulus interval through the insert earphones. Subjects were instructed to press the button when the lowest-volume tone was detected. The target tone occurred on 31% of the trials. Again, task position varied but was the same for both groups.

Scanning was performed parallel to the inferior orbitomeatal line, with the lowest plane positioned 10 mm above this line. Seven slices parallel to this plane, with their midpoints separated from each other by 13.8 mm, were obtained.

Task performance and motor responses were recorded during the scans. Accuracy and motor responses were tabulated at 2 and 5 minutes into each task. Because the task was begun 1 minute before injection, the 2-minute values reflect the interval starting 1 minute before the injection and ending 1 minute after the injection. Brain activity during this interval is heavily weighted in the determination of blood flow by this method.

Following scanning, subjects were questioned about their reactions to the procedures. Standard ratings of emotional reactivity (Profile of Mood States)[15] were completed.

Data Extraction

Four to five slices on each scan were chosen for analysis based on their resemblance to five standard planes with use of an atlas by a trained rater (A.C.K.) who was blind to the diagnosis and the hypotheses of the study. Before this, interrater reliability was established by comparing slice selections and regional measures performed by this and one other independent rater. Interrater reliability was found to be high (intraclass correlation coefficient, .98) (William E. Semple, PhD, unpublished data, 1986).

As illustrated in Fig 1, plane A, the most superior plane, is characterized by the presence of bilateral white-matter structures corresponding to a horizontal section of the corona radiata above the level of the corpus callosum. Plane B was selected as the plane just above the body of the corpus callosum. It contains the midcingulate region and bilateral white-matter strips. Plane C was defined by the presence of the body of the corpus callosum. The angular gyrus appears on this plane and is best sampled by the region labeled "left parietal" in Fig 2. Plane D, the basal ganglia plane, was defined by the prominent presence of the basal ganglia, internal capsule, and thalamus. The temporal lobes are also prominent at this level. Plane E, the lowest plane, was selected as the plane below the main basal ganglia plane, which contained lower frontal and temporal lobes. The hippocampal gyrus also appears at this level.[16]

Regional rates of cerebral blood flow were measured for 49 cortical regions of interest on these standard planes with use of the template shown in Fig 1. This template consisted of 45 7 × 7-pixel squares and four 7 × 13-pixel rectangles, which were placed on the resting scan with an image-analysis program that adjusts the placement of each box to maximize the value within each region sampled. The coordinates of the boxes were then saved and used to measure the same regions on the task-activated scans.

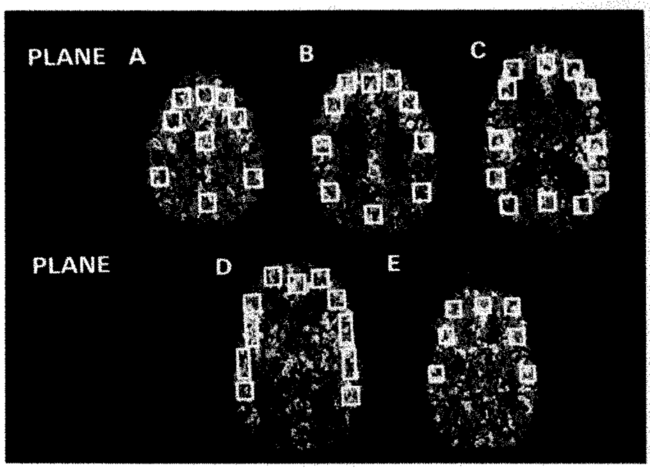

Fig 1.—*Samples of planes and regions of interest used in data extraction. Illustrated are the planes selected for analysis from a resting scan and the templates used to extract cerebral blood flow values.*

A global rate of cerebral blood flow was calculated for each state as an average of the gray matter–rich regions of interest on planes B through E. Plane A was not included, as not all subjects had an adequate match for this plane. To minimize the effects of interindividual and intraindividual variation in global blood flow, normalization was performed for each scan by dividing a subject's absolute blood flow rate for each region of interest by his global brain rate, a procedure similar in principle to the reference ratio or landscape method.[17] These normalized values constituted the raw data for statistical analysis. Whenever we refer to blood flow, we refer to these normalized values.

Statistical Analysis

Student's *t* tests and analyses of variance were used to test for differences in sample characteristics, performance, behavioral ratings, and physiologic measures. A one-way repeated-measures analysis of variance was used to test for differences in cerebral blood flow between resting and rhyming states within each group. Group differences in activation (in going from rest to rhyme detection and from rest to Continuous Performance Test) were tested with two-way repeated-measures analyses of variance that took group as a between-subject factor and state as a within-subject factor. Pearson product-moment correlation coefficients were used to examine relationships between degree of activation (defined by differences between rest and task) of temporoparietal regions on the rhyme task and behavioral measures.

Because the left parietal region on plane C best samples activity related to the angular gyrus based on atlas comparisons, this region was selected for hypothesis testing. Nonetheless, the entire cortical surface was examined to provide a more complete picture.

RESULTS

Sample

As shown in Table 1, the patients and controls were well matched (with no significant differences) on age, handedness, educational level, socioeconomic status, and WAIS-R Full Scale IQ or Performance IQ. Ten dyslexic subjects and 13 controls were 100% right-handed, one per group was 92% right handed, and three dyslexic subjects were 83% right-handed. Verbal IQ was depressed slightly in the dyslexic subjects relative to controls ($P<.05$) by deficits on subtests sensitive to educational achievement, such as information, vocabulary, and arithmetic, and those sensitive to heritable deficits in immediate auditory memory (Digit span). Paternal socioeconomic status was elevated (lower scores indicate higher social class) in the dyslexic group.

Highly significant deficits were documented in the dyslexic group across measures of reading, spelling, and math. Deficiencies in phonologic processing were documented with the GFW Reading of Symbols, a test that requires the reading of nonwords, forcing the reader to rely on phonologic rules.

Regional Cerebral Blood Flow

Resting State.—Cerebral blood flow in the baseline resting state was first examined for differences between the dyslexic and control groups. As expected, few differences were found. Dyslexic subjects and controls had equivalent blood flows to the left temporoparietal regions of greatest theoretical significance. Evaluating the rest of the brain, we found reduced blood flow to the right sylvian region and elevated blood flow to one medial frontal region in the dyslexic subjects compared with controls. Regional blood flow values for the resting state and for the rhyme detection scan are shown in Table 2.

Changes in Controls Elicited by Rhyme Detection.—As predicted, the rhyme detection task activated the left temporoparietal region near the angular gyrus (ie, the left parietal region on plane C) in the controls ($F=9.73$, $df=1,13$, $P<.01$), as illustrated in Fig 2. The "left middle temporal" region on plane D was also activated ($F=12.43$, $df=1,13$, $P<.01$). This likely reflects activity in Wernicke's area, which receives outflow from the angular gyrus.[18] In addition, one left posterior frontal region (plane B) ($F=5.04$, $df=1,13$) and two right temporoparietal regions (middle temporal, D plane: $F=5.74$, $df=1,13$; right parietal, C plane: $F=4.63$, $df=1,13$) were activated ($P<.05$), and the right sylvian region showed reduced blood flow relative to the resting state ($F=6.08$, $df=1,13$, $P<.03$) (Table 2).

Changes in Dyslexic Subjects Elicited by Rhyme Detection.—As shown in Fig 2 and documented in Table 2, dyslexic men activated the left anterior temporal region on plane D ($F=4.83$, $df=1,13$, $P<.05$) and the right temporal region on plane E ($F=4.58$, $df=1,13$, $P<.05$). A decrease in blood flow was seen in the medial frontal region on plane C ($F=10.96$, $df=1,13$, $P<.01$).

Differences Between Dyslexic Subjects and Controls in Activation During Rhyme Detection.—As illustrated in Fig 3 and documented in Table 2, dyslexic men showed significantly less activation than controls in the two left temporoparietal regions activated by rhyme detection in the controls (group × state, $P<.05$; left parietal, plane C: $F=5.23$, $df=1,26$; left middle temporal, plane D: $F=5.30$, $df=1,26$). Dyslexic subjects showed a nonsignificant decrease in the left parietal region on plane C and little change in the left middle temporal region on plane D. The three dyslexic subjects who were least strongly right-handed (having responded to two of 12 nonwriting items with the left hand, while no control responded this way on more than one of 12 items) fell within the range of the other (more strongly right-handed) dyslexic men in their activation of these two regions.

In the left posterior frontal region (inferior frontal cortex) and right anterior frontal region, both on plane D, significant group × state interactions indicated group differences in response to the task (left posterior frontal: $F=4.71$, $df=1,26$, $P<.04$; right anterior: $F=4.66$, $df=1,26$, $P=.04$). In both regions, controls showed a nonsignificant increase in response to the task, while dyslexic subjects showed a nonsignificant decrease in blood flow. Both left inferior frontal and right frontal regions have shown cortical anomalies in postmortem studies.[8] Dyslexic subjects showed greater activation in the left rolandic region (where dyslexic subjects showed increased blood flow and controls showed decreased blood flow) ($F=4.53$, $df=1,26$, $P=.04$) and in one lower right temporal region on plane E (where dyslexic subjects increased blood flow to a level nearly equal to that of the controls) ($F=6.15$, $df=1,26$, $P=.02$).

Performance Data.—Both groups performed with a high degree of accuracy (mean, >90%) on this intentionally easy task. Nonetheless, the dyslexic subjects' performance at 5 minutes was significantly depressed relative to controls, as shown in Table 3. The number of motor responses did not differ between groups and thus should not have contributed to the group differences that were seen.

Positron Emission Tomographic–Behavioral Correlations (Rhyme Detection).—To acquire a better understanding of the significance of the blood flow findings, correlations of blood flow variables and "dyslexia-related" behavioral variables were examined. To limit Type I error, only the nine regions of interest showing significant activation (when comparing rest with rhyme detection within groups) and/or group differences in activation were correlated with nine behavioral measures in the dyslexic subjects: WRAT-R Reading and Spelling, Gray Oral Reading scores, Verbal IQ, Verbal IQ–Performance IQ discrepancies, Digit span (a subtest of the WAIS-R), GFW Reading of Symbols (nonwords), and Finucci reading and spelling deviation quotients.

In dyslexic subjects, higher Verbal IQs were associated with greater (more normal) left parietal activation ($r=+.53$, $P<.05$). Finucci spelling quotients, which quantify discrepancies between IQ and spelling scores, were inversely correlated with activation in this region ($r=-.55$, $P<.05$). This inverse correlation was accounted for by the significant positive correlation with verbal IQ. Spelling and other scores entering into the Finucci equation were not significantly correlated with left parietal activation.

For the temporal cortex, greater deficits in Verbal IQ relative to Performance IQ (Verbal IQ–Performance IQ differences) were related to greater anterior temporal activation at a trend level ($r=-.47$, $P=.09$). Furthermore, shorter (more deficient) Digit span (a measure of immediate auditory memory shown to be heritable in dyslexia[19]) was associated with greater right middle temporal activation ($r=-.68$, $P<.01$). One possible interpretation is that the ability to activate left parietal cortex (activated in controls) is associated with less impairment, while activation of left anterior temporal and right middle cortex (not activated in controls) represent anomalous or compensatory activity and are associated with greater impairment. Given the restricted range of performance, it was not surprising that performance failed to correlate significantly with regional blood flow.

Table 2.—Rest and Rhyme Detection

	Normalized Regional Blood Flow Ratios, Mean (SD)			
	Controls (n=14)		Dyslexics (n=14)	
	Rest	Task	Rest	Task
Frontal cortex				
A plane				
Medial	1.03 (0.14)	1.03 (0.12)	1.05 (0.06)	1.09 (0.10)
R anterior	1.00 (0.09)	1.02 (0.10)	1.00 (0.10)	0.99 (0.10)
L anterior	0.99 (0.13)	0.94 (0.12)	1.04 (0.10)	1.03 (0.11)
R posterior	1.06 (0.08)	1.08 (0.10)	1.09 (0.11)	1.13 (0.12)
L posterior	1.04 (0.10)	1.02 (0.13)	1.03 (0.11)	1.06 (0.13)
B plane				
Medial	1.01 (0.17)	1.01 (0.15)	1.05 (0.08)	1.05 (0.11)
R anterior	1.03 (0.07)	1.00 (0.12)	1.02 (0.07)	1.06 (0.10)
L anterior	1.00 (0.09)	0.99 (0.14)	1.03 (0.06)	1.06 (0.10)
R posterior	1.03 (0.10)	1.04 (0.11)	0.99 (0.08)	1.01 (0.06)
L posterior	1.02 (0.12)	1.07 (0.12)*	1.04 (0.11)	1.07 (0.12)
C plane				
Medial	1.10 (0.09)	1.07 (0.08)	1.17 (0.07)†	1.10 (0.10)‡
R anterior	1.02 (0.06)	0.99 (0.10)	1.03 (0.07)	1.05 (0.12)
L anterior	1.01 (0.10)	0.99 (0.11)	1.02 (0.07)	1.06 (0.13)
R posterior	1.01 (0.10)	1.01 (0.11)	1.01 (0.07)	1.01 (0.12)
L posterior	1.02 (0.08)	1.03 (0.10)	1.02 (0.07)	0.99 (0.09)
D plane				
Medial	1.07 (0.09)	1.04 (0.07)	1.06 (0.12)	1.04 (0.17)
R anterior	0.92 (0.08)	0.96 (0.09)	0.99 (0.11)	0.93 (0.10)§
L anterior	0.95 (0.11)	0.91 (0.11)	1.00 (0.06)	0.96 (0.13)
R anterior	1.02 (0.13)	1.06 (0.15)	1.07 (0.13)	1.09 (0.12)
L posterior	0.99 (0.07)	1.05 (0.13)	1.08 (0.12)	1.06 (0.12)§
E plane				
Medial	1.01 (0.11)	0.99 (0.06)	1.00 (0.10)	1.01 (0.10)
R anterior	0.86 (0.08)	0.90 (0.10)	0.84 (0.09)	0.84 (0.08)
L anterior	0.87 (0.14)	0.84 (0.09)	0.82 (0.10)	0.84 (0.12)
R posterior	1.05 (0.13)	1.04 (0.16)	0.97 (0.13)	0.97 (0.11)
L posterior	0.99 (0.15)	1.01 (0.15)	1.01 (0.11)	1.01 (0.14)
Posterior cortex				
A plane				
Anterior medial	1.07 (0.05)	1.06 (0.12)	1.02 (0.07)	1.07 (0.12)
Posterior medial	1.01 (0.14)	0.98 (0.16)	1.07 (0.11)	1.02 (0.12)
R parietal	0.99 (0.12)	0.99 (0.13)	1.02 (0.10)	1.02 (0.13)
L parietal	0.98 (0.15)	1.00 (0.11)	0.99 (0.13)	0.99 (0.12)
B plane				
R rolandic	0.99 (0.08)	0.96 (0.11)	1.03 (0.12)	1.02 (0.13)
L rolandic	1.02 (0.07)	0.98 (0.08)	0.98 (0.11)	1.02 (0.12)§
R parietal	1.00 (0.08)	0.99 (0.08)	0.96 (0.07)	0.99 (0.09)
L parietal	1.02 (0.10)	0.97 (0.09)	0.97 (0.07)	0.93 (0.07)
Occipital	1.07 (0.08)	1.07 (0.14)	1.08 (0.06)	1.04 (0.12)
C plane				
R sylvian	1.11 (0.08)	1.02 (0.13)*	1.05 (0.06)†	1.01 (0.12)
L sylvian	1.09 (0.12)	1.12 (0.18)	1.05 (0.10)	1.08 (0.13)
R parietal	0.99 (0.07)	1.02 (0.08)*	1.01 (0.08)	1.02 (0.07)
L parietal	1.03 (0.12)	1.08 (0.10)‖	1.05 (0.14)	1.02 (0.11)§
R parieto-occipital	0.85 (0.11)	0.83 (0.12)	0.88 (0.12)	0.86 (0.15)
L parieto-occipital	0.88 (0.09)	0.84 (0.10)	0.87 (0.15)	0.87 (0.12)
Occipital	1.05 (0.09)	1.05 (0.10)	1.04 (0.11)	1.03 (0.13)
D plane				
R anterior temporal	1.14 (0.08)	1.13 (0.11)	1.10 (0.08)	1.12 (0.12)
L anterior temporal	1.10 (0.14)	1.12 (0.09)	1.09 (0.10)	1.15 (0.08)¶
R middle temporal	0.97 (0.11)	1.03 (0.09)*	1.00 (0.06)	1.00 (0.12)
L middle temporal	0.98 (0.09)	1.06 (0.08)‖	1.01 (0.06)	1.02 (0.07)§
R posterior temporal	0.93 (0.12)	0.90 (0.11)	0.90 (0.11)	0.84 (0.09)
L posterior temporal	0.95 (0.08)	0.91 (0.13)	0.93 (0.10)	0.90 (0.12)
E plane				
R temporal	0.94 (0.13)	0.93 (0.12)	0.89 (0.05)	0.94 (0.09)¶§
L temporal	0.93 (0.08)	0.95 (0.12)	0.92 (0.11)	0.96 (0.08)

*Regions changed by task in controls, $P<.05$.
†Dyslexics and controls differ in resting state, $P<.05$.
‡Regions changed by task in dyslexics, $P<.01$.
§Dyslexic-control differences in activation (group × state), $P<.05$.
‖Regions changed by task in controls, $P<.01$.
¶Regions changed by task in dyslexics, $P<.05$.

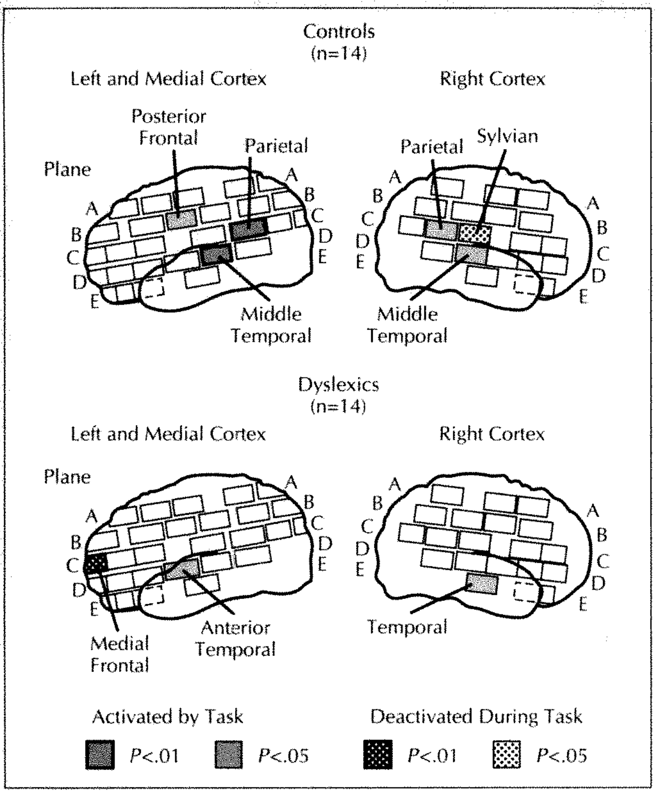

Fig 2.—*Regions activated by the rhyme detection task. Schematic representation shows statistically significant differences between rest and the rhyme detection scan. Regions labeled as medial on the figures at left were sampled from the medial portions of the cortex. The boxes outlined by broken lines are sampled from the surface of the frontal cortex medial to the temporal cortex.*

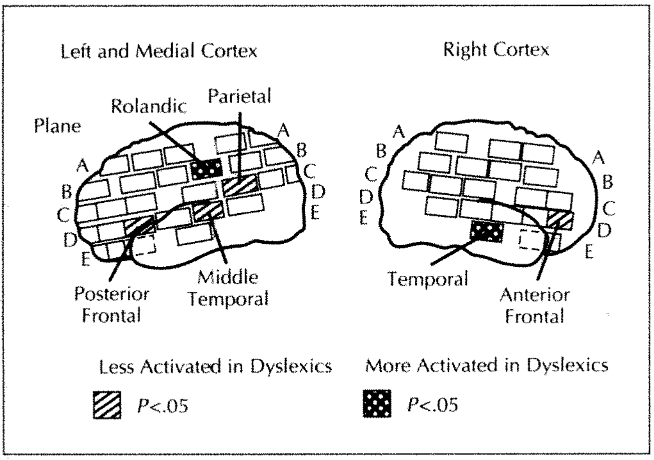

Fig 3.—*Differences in activation elicited by the rhyme detection task in dyslexic subjects vs controls. Schematic representation shows statistically significant group differences in activation (group × state interactions).*

Table 3.—Performance on Rhyme Detection

	Performance, Mean (SD)	
	Controls (n=14)	**Dyslexics (n=14)**
% Correct		
2 min	100 (2)	93 (12)
5 min	99 (2)	94 (8)*
No. of button presses		
2 min	8 (0.3)	8 (0.7)
5 min	20 (1.2)	19 (2.0)

*$P < .05$.

Changes in Blood Flow Elicited by Continuous Performance Test.—In contrast to the rhyme detection task, this task failed to activate any left-sided temporoparietal regions in controls but activated several right temporoparietal regions in controls and dyslexic subjects. In addition, in dyslexic subjects, it activated the same left anterior temporal region as was activated by rhyme detection (Table 4), suggesting that activation of this region is not specifically related to phonologic processing in dyslexia but rather is more generally related to auditory processing. Furthermore, activation of this region by rhyme detection was significantly correlated with activation by the Continuous Performance Test ($r = .66$, $P < .03$). Greater activation of this region on the Continuous Performance Test was related to greater deficits in Verbal IQ relative to Performance IQ ($r = -.63$, $P < .04$).

Pco_2 Values.—The Pco_2 values fell within the reference range, failed to differ between groups or states, and showed no significant group × state interactions.

Profile of Mood States.—Dyslexic subjects did not differ from controls on self-reports of emotional state during the scans. No differences were seen on any of the six subscales of the Profile of Mood States: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, or Confusion-Bewilderment.

COMMENT

To our knowledge, this is the first PET scan study to demonstrate left temporoparietal abnormalities in dyslexia. By employing a phonologic task—rhyme detection—that activated in normal readers regions hypothesized to be dysfunctional in dyslexia, we have demonstrated a failure of dyslexic subjects to activate left temporoparietal cortex, thereby suppporting the hypothesis of left temporparietal dysfunction in dyslexia.

Rhyme detection depends on phonologic awareness, an aspect of phonologic coding thought to constitute a core deficit in dyslexia. Phonologic awareness predicts success in learning to read, and phonologic coding is believed to be critical to the development of reading skills.[9,20] Twin studies suggest that deficits in phonologic coding, reading recognition, spelling skills, and digit span, a measure of immediate auditory memory, are inherited in dyslexia, while other reading-related skills—namely, reading comprehension, perceptual speed, and "orthographic coding" (nonphonologic knowledge of spelling conventions)—are not.[7,19] Other neuropsychological deficits associated with dyslexia may reflect normal individual variation or associated deficits not causally linked to reading impairment.[21] Thus, phonologic tasks, even more than reading per se, may provide the most relevant and sensitive probes for studies of brain function in dyslexia.

Rhyme detection tasks, both visual and auditory, activate the left temporoparietal cortex in the region of the angular gyrus, a region not activated by nonspeech sounds, such as clicks or tones.[22] The left temporoparietal regions activated in controls in this study by rhyme detection were not activated by an auditory attention task involving tones, replicating an earlier glucose study involving this task.[23] Thus, the failure to activate these re-

Table 4.—Rest and Continuous Performance Test-Temporoparietal Regions

	Normalized Regional Blood Flow Ratios, Mean (SD)			
	Controls (n=16)		Dyslexics (n=12)	
	Rest	Task	Rest	Task
Left				
C plane				
Sylvian	1.09 (0.12)	1.09 (0.12)	1.07 (0.10)	1.08 (0.09)
Parietal	1.02 (0.12)	1.01 (0.12)	1.02 (0.13)	1.02 (0.09)
D plane				
Anterior temporal	1.07 (0.09)	1.08 (0.14)	1.10 (0.09)	1.16 (0.09)*
Middle temporal	0.98 (0.08)	0.99 (0.10)	1.02 (0.06)	1.00 (0.07)
Posterior temporal	0.94 (0.08)	0.84 (0.10)†	0.94 (0.09)	0.91 (0.15)
E plane				
Temporal	0.91 (0.08)	0.89 (0.09)	0.93 (0.10)	0.89 (0.08)
Right				
C plane				
Sylvian	1.11 (0.10)	1.16 (0.14)	1.06 (0.07)	1.07 (0.16)
Parietal	1.00 (0.07)	1.05 (0.08)†	0.99 (0.08)	1.04 (0.07)*
D plane				
Anterior temporal	1.10 (0.09)	1.12 (0.10)	1.11 (0.08)	1.16 (0.12)
Middle temporal	0.96 (0.08)	1.06 (0.09)†	0.98 (0.07)	1.01 (0.11)
Posterior temporal	0.91 (0.12)	0.88 (0.14)	0.87 (0.09)	0.83 (0.08)
E plane				
Temporal	0.90 (0.12)	0.93 (0.09)	0.88 (0.05)	0.91 (0.07)

*Changed in dyslexics, $P<.05$.
†Changed in controls, $P<.01$.

gions in dyslexia is not likely due to differences solely in primary sensory processing.

A PET study of glucose metabolism in dyslexic adults failed to identify abnormalities in this region during serial reading of single words[24] but reported decreases of normal asymmetries in frontal and occipital regions. Possible reasons for discrepancies between these and our findings include the failure of the glucose study to employ a task shown to activate these regions in controls, as was done in our study, and the greater severity of our sample's reading deficits (mean fifth vs ninth grade reading levels). The use of ^{15}O-labeled water in our study permitted several states to be compared within subjects, providing a sensitive measure of activation, while the glucose study was restricted to a single state. Dyslexic subjects in the glucose study experienced the task as very easy, making virtually no errors during a 30-minute period, while our dyslexic subjects displayed mild deficits, despite the low level of difficulty of the rhyming task. Dyslexic adults, even those with minimal persisting reading impairment, continue to show deficits in nonword reading, a task that forces reliance on phonologic rules.[10] Thus, the ease with which the dyslexic subjects performed the task in the serial reading glucose study suggests the possibility that they were using other than a phonologic route to reading.

Serial word reading failed to activate the left angular/supramarginal region in normal readers in an earlier PET scan study of regional cerebral blood flow.[25] This was interpreted as supportive of "dual route theory," which hypothesizes the existence of two neural pathways underlying reading—one a phonologic route in which words are translated into their speech sound equivalents and the other involving direct links between visual word forms and word meanings without phonologic recoding. Serial word reading, therefore, may not adequately probe left angular/supramarginal functioning.

Our findings of temporoparietal involvement in dyslexia are consistent with those of a xenon inhalation study of regional cerebral blood flow in adults performing an orthographic task. In the orthographic task, subjects were required to listen to a string of words and to respond to each word whose correct spelling contained four letters.[26] Significant positive correlations were seen between performance accuracy and blood flow in a left superior temporal region (in or near Wernicke's area) in controls and in adults with childhood histories of dyslexia. Childhood reading impairment was related to excessive blood flow in a more posterior temporoparietal region, while adult reading outcomes were unrelated to blood flow in this region.

In the present study, greater (more normal) left temporoparietal activation was correlated with higher Verbal IQs in dyslexic adults. Because Verbal IQs in this group were selectively depressed by low scores on subtests sensitive to educational achievement, as well as to heritable deficits in auditory memory (Digit span), this correlation further supports a link between angular gyrus activity during phonologic processing and dyslexia. Unlike controls, dyslexic subjects activated an anterior left temporal region during both rhyme detection and the Continuous Performance Test, suggesting that this anomalous activity is not specifically related to phonologic processing. Activation of this region on both tasks was related to discrepancies between Verbal IQ and Performance IQ.

Regions other than the left temporoparietal regions of primary interest in this study may also be dysfunctional in dyslexia. Although not significantly activated by rhyme detection, dyslexic subjects differed from controls in their activation of a left inferior frontal and a right frontal region. All four male dyslexic brains studied post mortem have shown cortical anomalies in both left inferior frontal and posterior temporoparietal language regions, and some have shown these anomalies in right frontal regions as well.[8] Thus, tasks that activate language cortex anterior to the regions activated by rhyme detection and tasks that activate right frontal cortex are also of interest as probes of these regions.

Dyslexic subjects also showed significantly increased activation in one right temporal region. Neuropathologic studies of dyslexia have shown unusual symmetry in the usually asymmetrical planum temporale, a region on the supratemporal plane that is important for language functioning. This region, which is generally larger on the left side, was highly symmetrical in all seven dyslexic brains studied post mortem due to an increase in size on the right side,[8,27] a finding recently corroborated by an magnetic resonance imaging study of dyslexic adolescents.[28] Galaburda and his colleagues[8] have postulated that this increase is due to a reduction of normal cell death during brain development, with excessive cell survival on the right side. While the implications for function are uncertain, excessive cells may form anomalous connections, resulting in a "miswiring" of the brain in dyslexia that affects the function of regions remote from the primary "lesion." Thus, we are also examining the function of right temporoparietal regions with tasks that activate them.

Methodologic limitations of this study include the size of the effects and intraindividual and interindividual variability. The auditory rhyme detection task used here elicited increases of 5% to 8% in the left temporoparietal cortex of controls. Group differences in the degree of activation were equally subtle and fell in the 7% to 8% range. The size of these effects may have been reduced by our method of data extraction, which maximized values obtained from the baseline resting scans. However, smaller changes (of this magnitude) are generally seen with auditory tasks relative to visual or tactile stimulations with PET.[22] Repeated testing of subjects under the same conditions to improve reliability or more sensitive analytic techniques may enhance our ability to detect subtle differences in brain function in developmental disorders.

In summary, using PET with ^{15}O-labeled water, we have shown subtle deficits in activation in left temporoparietal cortex in dyslexia during the performance of a phonologic task that activates these regions in controls. This supports the hypothesized involvement of these regions in developmental dyslexia and the value of neuropsychological probes in the functional neuroimaging of developmental disorders.

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Albendazole Therapy for Giant Subarachnoid Cysticerci

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• **Albendazole is considered to be the drug of choice for treatment of parenchymal brain cysticercosis. Its efficacy, however, for treatment of subarachnoid cysticerci has not been established, to our knowledge. In this study, we treated four patients who had giant subarachnoid cysticerci with albendazole at daily doses of 15 mg/kg of body weight for 8 days. Computed tomographic studies showed that all cysts disappeared 3 months after the end of treatment. This was associated with marked clinical improvement in every case. Our results indicated that albendazole is highly effective for treatment of this form of the disease.**

(*Arch Neurol.* 1992;49:535-538)

Albendazole is an imidazole with intense antiparasitic properties.[1,2] Previous studies, performed by us[3-6] and other investigators,[7,8] have demonstrated its therapeutic efficacy for treatment of parenchymal brain cysticercosis, and now, albendazole is considered to be the drug of choice for treatment of this form of the disease.[9-11] In contrast, therapy for subarachnoid cysticercosis has been limited to symptomatic treatment, with surgical intervention used in patients with giant cysts.[12,13] In 1990, we described a patient with multiple subarachnoid cysticerci in whom an adequate response to albendazole was achieved.[14] Such a report, together with a recent study that showed that albendazole reached a high concentration in cerebrospinal fluid,[15] led us to evaluate the efficacy of albendazole therapy for giant subarachnoid cysticerci.

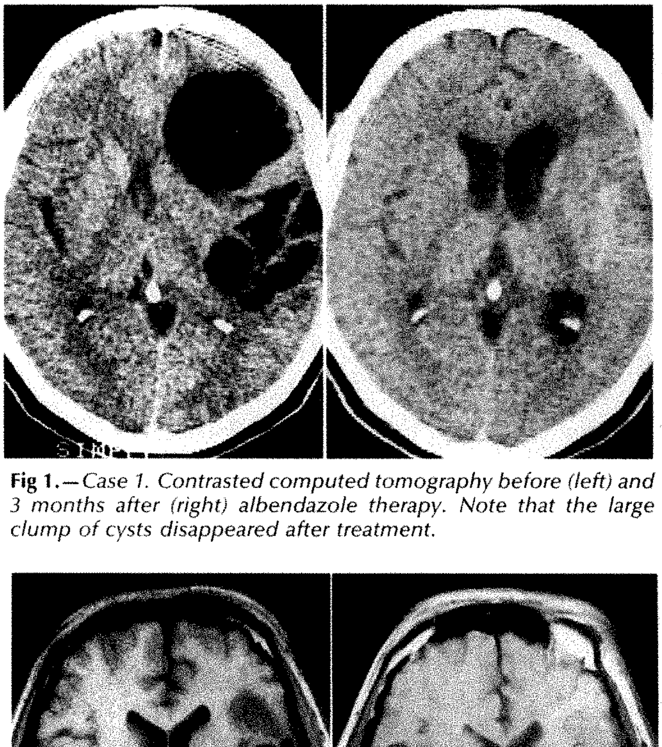

Fig 1.—*Case 1. Contrasted computed tomography before (left) and 3 months after (right) albendazole therapy. Note that the large clump of cysts disappeared after treatment.*

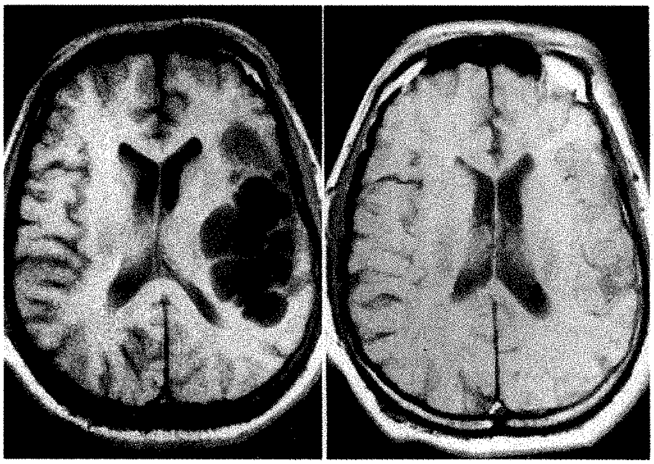

Fig 2.—*Case 2. T_1-weighted (repetition time, 500 ms/echo time, 21 ms) magnetic resonance imaging before (left) and 3 months after (right) albendazole therapy. The giant cyst disappeared after treatment.*

PATIENTS AND METHODS

Four patients with giant subarachnoid cysticerci were treated with albendazole at a daily dose of 15 mg/kg of body weight for 8 days. Two of these patients (cases 1 and 2) were seen at the National Institute of Neurology and Neurosurgery of Mexico, Mexico City, and the other two patients (cases 3 and 4) were seen at the Regional Hospital of the Ecuadorian Institute of Social Security of Guayaquil (Ecuador). In each case, the diagnosis had been confirmed by computed tomographic (CT) findings of a multilobulated, hypodense lesion that measured more than 5 cm in diameter, which is characteristic of this type of *Cysticercus*[16]; one patient was also examined with magnetic resonance imaging. In addition, two patients (cases 1 and 2) had cerebrospinal fluid analysis that showed positive immunologic reactions to anti-cysticercal antibodies by enzyme-linked immunosorbent assay,[17] and two patients (cases 3 and 4) had CT evidence of parenchymal brain cysticerci.

The four patients were men, with ages ranging from 34 to 51 years. They had a chronic neurologic picture characterized by seizures, focal signs, and intellectual deterioration from 6

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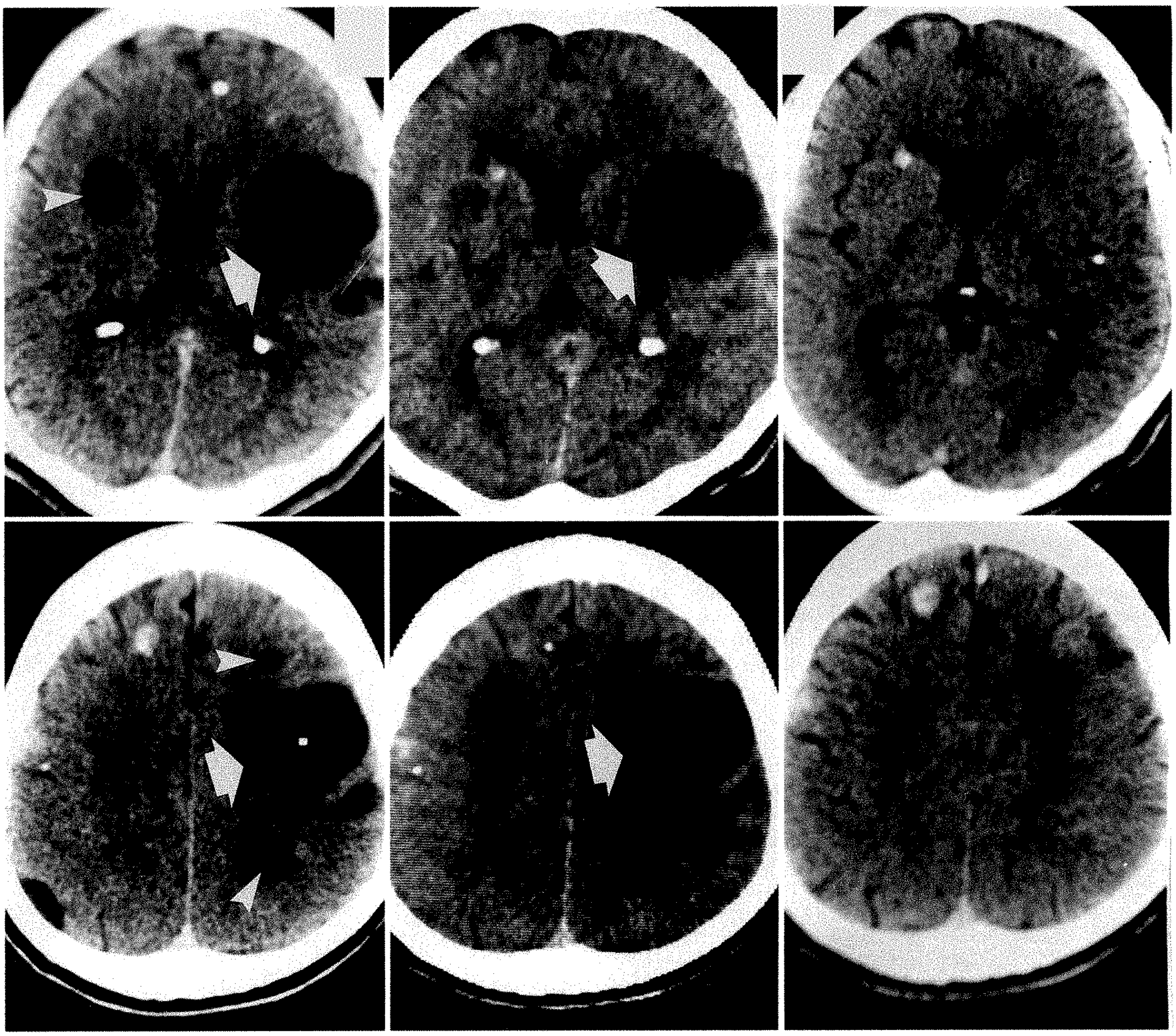

Fig 3.—*Case 3. Top left and bottom left, Contrasted computed tomographic scans before therapy show a large subarachnoid cyst (white arrow) and parenchymal cysticerci (white arrowheads). Top center and bottom center, Computed tomographic scans 3 months after praziquantel therapy and before albendazole therapy. Note that the parenchymal cysts have disappeared, but the giant subarachnoid cyst was unchanged (white arrow). Top right and bottom right, Computed tomographic scans 3 months after albendazole therapy show complete resolution of the giant subarachnoid* Cysticercus.

months to 5 years before admission. Simple partial seizures with or without secondary generalization were recorded in three patients (cases 1, 3, and 4). In two of these patients, therapy with anticonvulsants had been started 6 and 8 months before the albendazole trial, and both patients had recurrent seizures despite therapeutic blood levels of such drugs. All four patients had hemiparesis contralateral to the giant cyst that developed during a period of months in every case. In addition, two patients (cases 2 and 4) had progressive decline of mental status, mostly characterized by a reduced interest in social activities, memory disturbances, and emotional lability. No patient had papilledema before the trial.

Besides albendazole, all patients received a simultaneous course of dexamethasone phosphate at dosages of 4 mg every 6 to 8 hours. Treatment with dexamethasone was started from 2 to 4 days before albendazole administration, and its use was prolonged until a few days after the trial had been completed. Intermittent doses of (20%) mannitol were used if patients had clinical evidence of increased intracranial pressure during the course of albendazole. Antiepileptic drugs were continued during the trial for all patients who had been receiving them before this study. In addition, analgesics and antiemetics were used, as needed.

Evaluation of therapeutic response to albendazole consisted of the objective comparison of the size of the cyst that was shown by CT scans or magnetic resonance imaging before and 3 months after the end of treatment. Neurologic status was evaluated before, during, and after the trial for every patient, and any change was recorded. The same neurologist (O.H.D.) examined all the patients and reviewed the neuroimaging studies before and after the trial. In this way, the protocol of study was the same as that previously used by us for the evaluation of anti-cysticercal drugs.[3-6,9,18]

RESULTS

Differences on neuroimaging studies obtained before and 3 months after the end of treatment showed the ef-

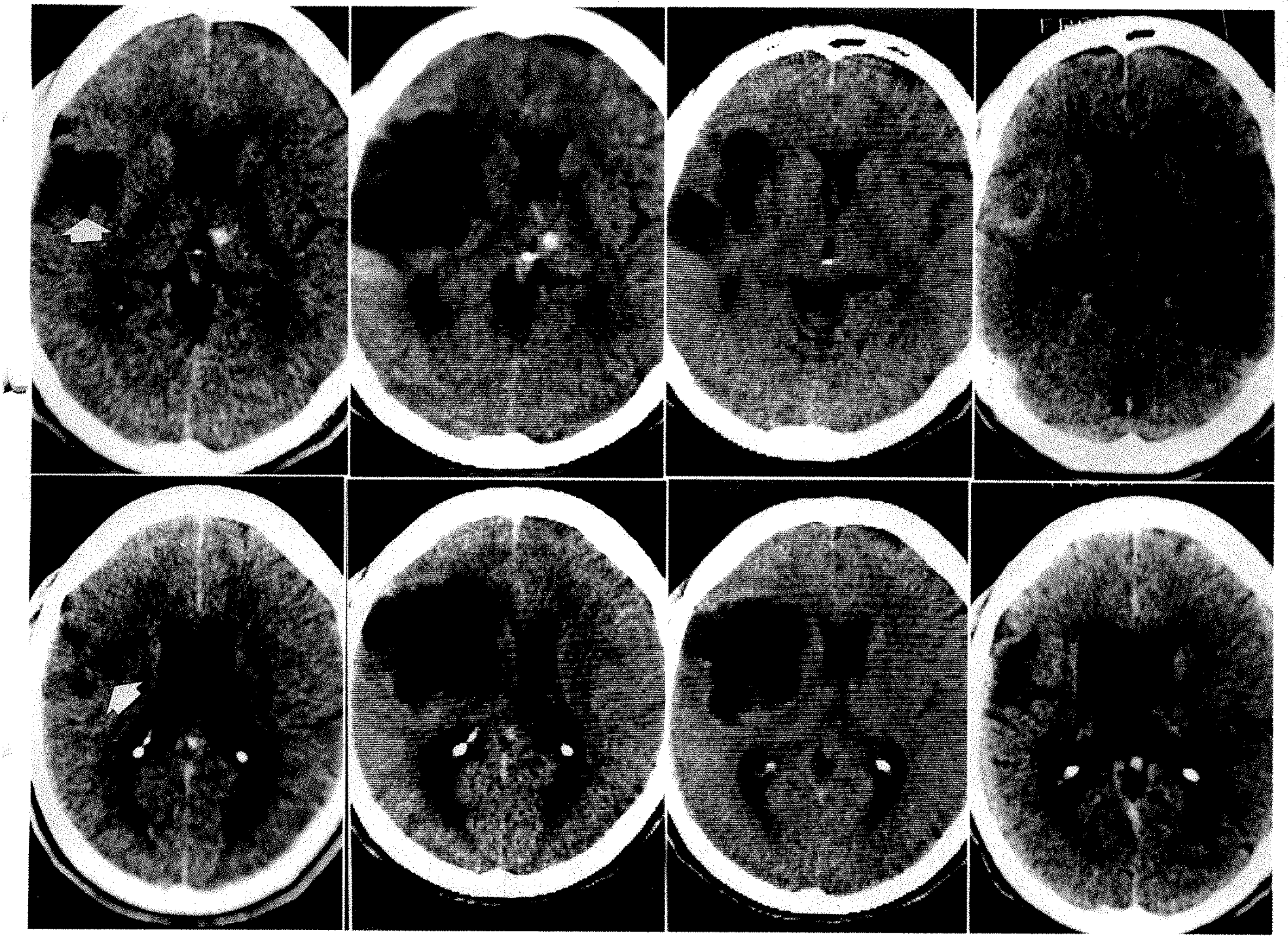

Fig 4.—*Case 4. Top left and bottom left, Contrasted computed tomographic scans 6 months before albendazole therapy show a subarachnoid* Cysticercus *(white arrow). Top left center and bottom left center, Computed tomographic scans on the day before albendazole therapy. Note the marked increase in the size of the cyst and the displacement of midline structures. Top center right and bottom center right, Computed tomographic scans on the last day of treatment with albendazole. The giant cyst reduced in size. Top right and bottom right, Computed tomographic scans 3 months after therapy show disappearance of the giant cyst.*

fectiveness of albendazole for subarachnoid cysticerci (Figs 1 and 2). One patient (case 3) had previously been treated with praziquantel, and a CT scan that was performed 3 months after that trial had been completed showed resolution of parenchymal cysts but persistence of the giant subarachnoid cysticerci. This patient was selected for the albendazole trial 3 months after praziquantel therapy, when no further changes on the CT scan could be expected as the result of this drug[19]; 3 months after albendazole therapy, the CT scan showed total resolution of the subarachnoid *Cysticercus* (Fig 3). Another patient (case 4) served as his own control, since he had a CT scan performed 6 months before the course of albendazole. Comparison of CT scans, 6 months and on the day before starting albendazole therapy, showed a marked increase in the size of the cyst. Three months later, however, the giant cyst had disappeared as the result of therapy (Fig 4).

During the course of albendazole, the four patients experienced headache and vomiting. These symptoms were ameliorated with analgesics and antiemetics in three patients. In the remaining patient, four doses of 100 mL of 20% mannitol were needed for relief of symptoms. Two patients (cases 2 and 3) had transient worsening of the hemiparesis during the trial, and another patient (case 4) had a bout of simple partial seizures associated with psychotic changes. These complaints were self-limited and resolved after a few days in every case. Clinical follow-up by the end of the study showed that the condition of all patients improved. The three patients with seizures continued to receive anticonvulsant therapy and were completely free of seizures after the trial. The motor deficit gradually improved in every case. Finally, the two patients with intellectual deterioration returned to their work and showed marked improvement in social compliance after therapy.

COMMENT

Results of this study suggest that albendazole is a useful drug for treatment of subarachnoid cysticercosis. The drug produced a complete disappearance of giant cysts, as demonstrated on neuroimaging studies, that was associated with a marked clinical improvement in every case. Effectiveness of albendazole therapy was emphasized in patient 3, in whom a previous course of praziquantel failed to destroy the giant cyst (Fig 3), and in patient 4, in whom CT scans that were performed 6 months and on the day before the trial showed how these lesions may grow if they are left untreated (Fig 4).

Our patients received a simultaneous course of dexamethasone to ameliorate the inflammatory reaction that was developed by the host in response to the destruction of parasites. Otherwise, such a reaction could cause occlusive endarteritis of small penetrating vessels around the cysts.[20,21] We believe that the concomitant administration of dexamethasone is mandatory when treating patients who have subarachnoid cysticercosis with albendazole. This association should not create concern because it has been demonstrated that plasma levels of albendazole are increased by dexamethasone.[22] These findings are in contrast with those observed with praziquantel, for which the routine association with steroids is not recommended[23,24] because its plasma levels are lowered by dexamethasone.[25]

Albendazole has a different chemical structure than praziquantel and perhaps a different mechanism of action. While praziquantel produces spastic paralysis of the parasite musculature and destroys the scolex,[26] albendazole inhibits the uptake of glucose by parasitic membranes, thus causing an energy depletion in them.[27] Such differences may explain why albendazole (but not praziquantel) is effective in the treatment of giant subarachnoid cysticerci, which are usually composed of several membranes that are arranged like a cluster of grapes without a scolex.[28,29]

Some authors have questioned the value of anticysticercal drugs, and they have even been opposed to their use at all.[30,31] Nevertheless, several studies have shown that anti-cysticercal drugs not only eradicate CT evidence of cysticerci, but also produce marked clinical improvement in many cases.[9,32,33] The results of our study reinforce these findings and provide further evidence that albendazole may obviate the need of surgery in some patients with giant subarachnoid cysticerci.

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ANNOUNCING

Acute migraine pain relief...

From a nasal spray

Mead Johnson Laboratories
introduces the only nasal spray analgesic

New STADOL® NS™

(butorphanol tartrate) Nasal Spray

A Potent Analgesic

- Synthetically derived opioid analgesic with sedative properties*
- Efficacy comparable to IM meperidine
- Onset of pain relief within 15 minutes[1]

Effective in Acute Pain

- Demonstrated efficacy in relief of acute migraine pain[1]
- Relieved the acute pain of migraine unresponsive to specific abortive agents[1]
- Also proven effective in the relief of acute pain following invasive surgical procedures[2]
- The most frequently reported adverse effects are: somnolence (43%), dizziness (19%), and nausea/vomiting (13%)

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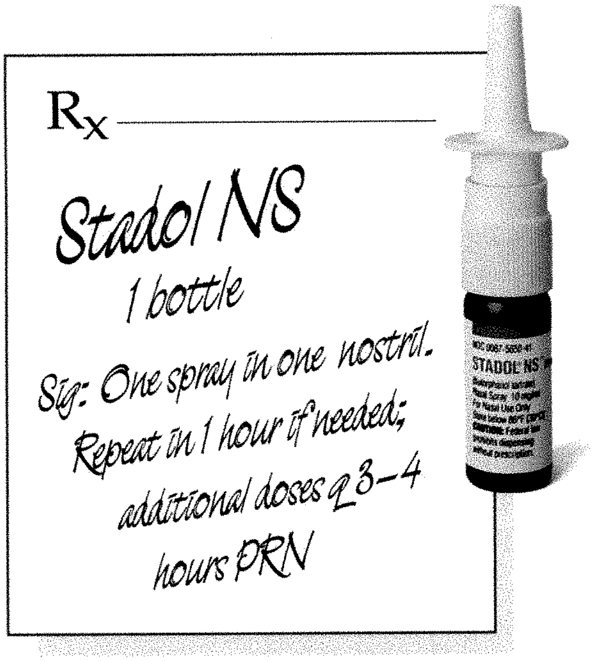
A Convenient New Dosing Form

- An alternative to oral opioids with the efficacy of injectable analgesics
- Easily and comfortably self-administered
- Not a federally controlled substance

Simple, Flexible Dosing

- Initial dose is 1 mg–one spray in one nostril
- An additional 1-mg dose may be taken in 60 minutes if needed[†]
- Dosing may be repeated in 3 to 4 hours



Rx

Stadol NS

1 bottle

Sig: One spray in one nostril.
Repeat in 1 hour if needed;
additional doses q 3–4
hours PRN

Acute Pain Relief, Delivered in Minutes

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*Patients should not perform potentially hazardous tasks (eg, driving, operating machinery). Alcohol should not be consumed while using butorphanol.

[†] Depending on the severity of pain, an initial dose of 2 mg (one spray in each nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs.

Please see next page for brief summary of prescribing information.

C-K54-2-92

STADOL® NS™

(butorphanol tartrate) Nasal Spray

Acute Pain Relief, Delivered in Minutes

Brief Summary

INDICATIONS
STADOL® NS™ (butorphanol tartrate) Nasal Spray is indicated for the management of pain when the use of an opioid analgesic is appropriate.

CONTRAINDICATIONS
STADOL NS is contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride.

WARNINGS

Patients Dependent on Narcotics
Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

PRECAUTIONS

Head Injury and Increased Intracranial Pressure
As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control
Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease
In patients with severe hepatic or renal disease the initial dosage interval for STADOL NS should be increased to 6-8 hours until the response has been well characterized. Subsequent doses should be determined by patient response rather than being scheduled at fixed intervals.

Cardiovascular Effects
Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Drug Interactions
Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (cimetidine, erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

The fraction of STADOL NS absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if STADOL NS is administered concomitantly with, or immediately following, a nasal vasoconstrictor.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Use in Ambulatory Patients
Drowsiness and dizziness related to the use of butorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc.). Patients should be told to use caution in such activities until their individual responses to butorphanol have been well characterized.

Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects.

Patients should be instructed on the proper use of STADOL NS.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of butorphanol has not been adequately evaluated.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/sq.m.) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/sq.m.) subcutaneous dose.

Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation.

Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. Pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/sq.m.) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (5.1 mg/sq.m.) and 60 mg/kg/oral (10.2 mg/sq.m.) also showed higher incidences of post implantation loss in rabbits.

Labor and Delivery
STADOL NS is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

Nursing Mothers
Butorphanol has been detected in milk following administration of STADOL Injectable to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 microgram/liter of milk in a mother receiving 2 mg IM four times a day).

Although there is no clinical experience with the use of STADOL NS in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

Pediatric Use
Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use
Initially a 1 mg dose of STADOL NS should generally be used in geriatric patients and 90-120 minutes should elapse before deciding whether a second 1 mg dose is needed.

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65. Elderly patients may be more sensitive to its side effects. Results from a long-term clinical safety trial suggest that elderly patients may be less tolerant of dizziness due to STADOL NS than younger patients.

ADVERSE REACTIONS
A total of 2446 patients were studied in butorphanol clinical trials. Approximately half received STADOL Injectable with the remainder receiving STADOL NS. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short- and long-term clinical trials in patients receiving butorphanol by any route and from post-marketing experience with STADOL Injectable. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo treated patients in controlled trials.

REACTIONS
The most frequently reported adverse experiences across all clinical trials with STADOL Injectable and STADOL NS were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with STADOL NS only, nasal congestion (13%) and insomnia (11%) were frequently reported.

The following adverse experiences were reported at a frequency of 1% or greater, and were considered to be probably related to the use of butorphanol:

BODY AS A WHOLE: asthenia/lethargy*, headache*, sensation of heat

CARDIOVASCULAR: VASODILATION*, PALPITATIONS

DIGESTIVE: ANOREXIA*, CONSTIPATION*, dry mouth*, nausea and/or vomiting (13%), stomach pain

NERVOUS: anxiety, confusion*, dizziness (19%), euphoria, floating feeling, INSOMNIA (11%), nervousness, paresthesia, somnolence (43%), TREMOR

RESPIRATORY: BRONCHITIS, COUGH, DYSPNEA*, EPISTAXIS*, NASAL CONGESTION (13%), NASAL IRRITATION*, PHARYNGITIS*, RHINITIS*, SINUS CONGESTION*, SINUSITIS, UPPER RESPIRATORY INFECTION*

SKIN AND APPENDAGES: sweating/clammy*, pruritus

SPECIAL SENSES: blurred vision, EAR PAIN, TINNITUS*, UNPLEASANT TASTE* (also seen in short-term trials with STADOL® NS™ [butorphanol tartrate] Nasal Spray)

(Reactions occurring with a frequency of 3-9% are marked with an asterisk.* Reactions reported predominantly from long-term trials with STADOL NS are CAPITALIZED.)

The following adverse experiences were reported with a frequency of less than 1%, in clinical trials or from post-marketing experience and were considered to be probably related to the use of butorphanol.

CARDIOVASCULAR: hypotension

NERVOUS: abnormal dreams, agitation, *drug dependence*, dysphoria, hallucinations, hostility

SKIN AND APPENDAGES: rash/hives

UROGENITAL: impaired urination

(Reactions reported only from post-marketing experience are *italicized.*)

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term STADOL NS trials and from post-marketing experiences under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

BODY AS A WHOLE: edema

CARDIOVASCULAR: hypertension

NERVOUS: *convulsion, delusions,* depression

RESPIRATORY: *apnea,* shallow breathing

(Reactions reported only from post-marketing experience are *italicized.*)

DRUG ABUSE AND DEPENDENCE
Although the mixed agonist-antagonist opioid analgesics, as a class, have lower abuse potential than morphine, all such drugs can be and have been reported to be abused.

Chronic use of STADOL Injectable has been reported to result in mild withdrawal syndromes, and reports of overuse and self-reported addiction have been received.

Among 161 patients who used STADOL NS for 2 months or longer approximately 3% had behavioral symptoms suggestive of possible abuse. Approximately 1% of these patients reported significant overuse. Symptoms such as anxiety, agitation, and diarrhea were observed. Symptoms suggestive of opioid withdrawal occurred in 2 patients who stopped the drug abruptly after using 16 mg a day or more for longer than 3 months.

Special care should be exercised in administering butorphanol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is necessary, such patients should be closely supervised.

OVERDOSAGE

Clinical Manifestations
The clinical manifestations of overdose are those of opioid drugs, the most serious of which are hypoventilation, cardiovascular insufficiency and/or coma.

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment
The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

DOSAGE AND ADMINISTRATION
Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, patients with hepatic or renal disease or in labor requires extra caution (see PRECAUTIONS). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60-90 minutes, an additional 1 mg dose may be given.

The initial two dose sequence outlined above may be repeated in 3-4 hours as needed.

Depending on the severity of the pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients single additional 2 mg doses should not be given for 3-4 hours.

Safety and Handling
STADOL NS is an open delivery system with increased risk of exposure to health care workers.

In the priming process, a certain amount of butorphanol may be aerosolized, therefore the pump sprayer should be aimed away from the patient or other people or animals.

The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED
STADOL NS is supplied in a child-resistant prescription vial containing a metered-dose spray pump and protective clip with dust cover, a bottle of nasal spray solution, and a patient instruction leaflet. On average, one bottle will deliver 14-15 doses if no repriming is necessary.

NDC 0087-5650-41: 10 mg per mL, 2.5-mL bottle.

Storage Conditions
Store below 86°F (30°C). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CAUTION: Federal law prohibits dispensing without prescription.

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2. Data on file, Bristol-Myers Squibb Company.

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Original Contribution

Technetium-99m HM-PAO Single Photon Emission Computed Tomography Imaging in Transient Global Amnesia

Patrice Laloux, MD; Christine Brichant, MD; Francisca Cauwe, BSc; Patrick Decoster, MD

• Five right-handed patients with pure transient global amnesia were evaluated with technetium-99m hexamethylpropyleneamine oxime single photon emission computed tomography after the amnesic attack. Independent of the interval between the procedure and the amnesic episode, single photon emission computed tomography demonstrated a decreased cerebral blood flow in the left temporal lobe in one patient and in the left parietotemporal region in three patients, with a more marked reduction in the temporal lobe. The remaining three patients were normal. A control single photon emission computed tomographic study was carried out in one patient 3 months after the amnesic attack and showed a left-sided persistent temporal hypoperfusion. These findings suggest that in some patients, transient global amnesia can be due to a vascular mechanism requiring strong investigations for vascular risk factors and appropriate treatment. During a follow-up period of 12 to 32 months, none of the patients with regional hypoperfusion suffered cerebrovascular events, suggesting that single photon emission computed tomography has no predictive value for further stroke.

(*Arch Neurol.* 1992;49:543-546)

Transient global amnesia (TGA), a syndrome affecting patients in middle age or beyond, is characterized by a sudden memory loss of recent events, transient inability to retain new information, and retrograde amnesia of variable extension. Complete recovery is usual within a few hours, leaving the patient with no disability other than amnesia for the events occurring during the attacks.[1-3] Although transient memory dysfunction has been reported in association with vertebrobasilar symptoms,[4-14] TGA should be defined as a pure transient amnesia without other neurologic symptoms or signs and without fixed deficits.[15] Transient global amnesia is commonly thought to be due to bilateral hippocampal dysfunction,[5,9,11,16-22] but the exact mechanism remains controversial. Although TGA has been mentioned in various neurologic conditions,[8,14,23] such as epilepsy,[24,25] migraine,[5,8,15,26-30] or mass lesions,[14,31-40] most reports have emphasized a mechanism of unilateral or bilateral transient ischemia in the territory of the posterior cerebral circulation.[7-9,11,13,29-30,41,42] Brain computed tomography (CT) rarely demonstrates focal ischemic lesions,[4,9,10,43,44] and studies of cerebral blood flow (CBF) during or after the amnesic attack are rare. We describe five patients with TGA in whom technetium-99m hexamethylpropyleneamine oxime (HM-PAO) single photon emission computed tomography (SPECT) was carried out after the amnesic episode.

SUBJECTS AND METHODS

Between June 1988 and February 1991, we retrospectively and prospectively studied five patients presenting with TGA as defined by the following criteria[15,44]: (1) transient amnesic attack with no direct relation to cranial trauma or whiplash, (2) evidence given by a witness of the inability to form new memories, (3) repetitive queries, (4) apparently normal behavior and orientation, (5) evidence given by a witness of normal long-term memory, and (6) presence of retrograde amnesia at least during the episode and absence of other neurologic signs or symptoms. Each patient underwent a neurologic examination and standard neuropsychological testing (Mini-Mental State score, Rey auditory learning, visual learning, evocation of recent and remote events, Luria's tests, speech, auditory comprehension, writing, reading, oral and written calculation, limb praxias, and drawing of a cube), but none of them could be examined by a neurologist during the acute episode. Risk factors for cerebrovascular disease were evaluated: hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >110 mm Hg), history of coronary heart disease, hypercholesterolemia (>7.24 mmol/L [280 mg/dL]), cigarette smoking within the last 10 years, diabetes mellitus, and alcohol consumption. The following investigations were obtained: laboratory tests, electroencephalogram (EEG), Doppler ultrasound study and digital intravenous angiography of the extracranial arteries, electrocardiogram, transthoracic bidimensional echocardiography in three patients (patients 1, 4, and 5), and 24-hour electrocardiographic Holter monitoring in four patients (patients 1, 3, 4, and 5). Brain CT with and without contrast was performed in all patients at least 48 hours after onset, with an interval between 2 and 4 days. Single photon emission computed tomography using technetium-99m HM-PAO (7.4 MBq) was carried out with a rotating gamma

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Presented at the Fifth Toronto (Ontario) Stroke Workshop, September 12, 1990.

Reprint requests to Department of Neurology, Mont-Godinne University Hospital, B-5530 Yvoir, Belgium (Dr Laloux).

Table 1.—Clinical Presentation of Patients With Transient Global Amnesia*

Patient No./ Age, y/Sex	Vascular Risk Factors	Duration of Episode, h	Neurologic Examination	Other Findings
1/50/M	Hypertension	2	N	. . .
2/60/F	Hyperlipidemia	4	N	Angiography: nonstenotic plaques in R ICA
3/63/F	Hypertension	4	N	Angiography: bilateral nonstenotic plaques in ICA
4/65/M	Hypertension, myocardial infarction	16	N	ECG: LVH; echocardiogram: anteroinferior hypokinesia
5/67/M	Hypertension	1	N	ECG: LBBB, RBBB; angiography: bilateral nonstenotic plaques in ICA

*N indicates normal; ICA, internal carotid artery; ECG, electrocardiogram; LVH, left ventricular hypertrophy; LBBB, left bundle-branch block; and RBBB, right bundle-branch block.

camera (General Electric, Milwaukee, Wis, 64 projections of 30 seconds each). No study could be performed during the acute episode. The examinations took place 1 to 4 days (cases 3 through 5), 6 weeks (case 1), or 18 months (case 2) after the onset of the amnesic attack. In one patient (case 4), SPECT was repeated after 3 months. Data were reconstructed to obtain consecutive parallel axial slices every 12 mm parallel to and above the orbitomeatal line. Coronal and sagittal slices were also reconstructed. On each axial slice, 12 symmetric regions of interest were considered, six over each hemisphere. The regions of interest (3 × 3 pixels) were located on the cortical ribbon, two in the anterior, four in the middle, and two in the posterior areas. In each region of interest, the differences in total count were expressed as a percentage of the values from the contralateral hemisphere with a normal CBF. Interhemispheric differences of at least 5% were considered to be significant.

RESULTS

Five right-handed patients, three men and two women, were studied (Table 1). Their mean age was 61 years old. All patients had their first attack at the time of the admission. All symptoms lasted less than 24 hours (1 to 16 hours), without remaining disability other than amnesia of the episode. During the attack, no patient complained of other neurologic symptoms. No precipitating factors were noted. In four patients, the amnesic attack suddenly occurred at home without any strenuous activity, and in one case it occurred while the patient was driving a car (case 3). Hypertension was present in four patients, coronary heart disease with history of myocardial infarction in one patient, and hypercholesterolemia in one patient. Cigarette smoking, diabetes mellitus, and alcohol consumption were not reported. No patient had suffered prior transient ischemic attack (TIA), stroke, epilepsy, or migraine. Results of neurologic and general examinations, standard neuropsychological testing, and laboratory tests were entirely normal in all patients. Heart investigations did not show any emboligenic cardiopathy. Doppler ultrasound and intravenous angiography of the extracranial arteries disclosed nonstenotic atheromatous plaques in the internal carotid artery in three patients (cases 2, 3, and 5) associated with a normal vertebrobasilar circulation. Electroencephalography and brain CT were normal in all patients (Table 2). Whatever the interval between the procedure and the amnesic episode, SPECT demonstrated a decreased CBF in the left temporal lobe in one patient (case 4) and in the left parietotemporal region in three patients (cases 2, 3, and 5), with a more marked reduction in the temporal lobe, and was normal in the remaining patient (case 1; Figure). A control SPECT examination was repeated in one patient (case 4) 3 months after the amnesic attack and showed a left-sided persistent temporal hypoperfusion (Table 2). All patients were discharged from the hospital receiving acetylsalicyclic acid, 500 mg/d. During a follow-up period of 12 to 32 months, none of them presented with TIA, stroke, or recurrent TGA.

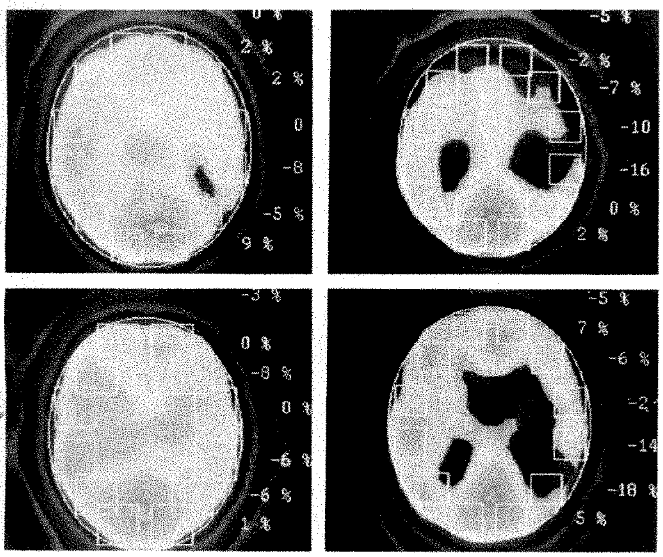
Table 2.—Results of Laboratory Tests and Follow-up in Patients With TGA*

Patient No.	EEG	Brain CT	Time of SPECT Following TGA	SPECT	Follow-up, mo	Cerebrovascular Events During Follow-up
1	N	N	6 wk	N	12	None
2	N	N	18 mo	L TP	32	None
3	N	N	4 d	L TP	32	None
4	N	N	1 d, 3 mo	L T, L T	15	None
5	N	N	4 d	L TP	22	None

*TGA indicates transient global amnesia; EEG, electroencephalography; CT, computed tomography; SPECT, single photon emission CT; N, normal; L TP, hypoperfusion in the left temporoparietal region, more marked in the temporal lobe; and L T, hypoperfusion restricted to the left temporal lobe.

COMMENT

None of our five patients was examined during the acute amnesic episode, but the information provided by their family or physician corresponded to the strict diagnostic criteria of TGA proposed by Caplan et al.[15] Although a connection between TGA and migraine has been reported,[15,26-30] none of our patients had migraine before or during the amnesic episode. Neurologic examination and neuropsychological testing showed no persistent memory loss or clinical signs of focal ischemic disturbances. Although EEG and brain CT were normal, technetium-99m HM-PAO SPECT demonstrated a left-sided temporoparietal hypoperfusion in four of our five patients, whatever the interval between the procedure and the amnesic attack. The decreased CBF was either restricted in the left temporal lobe in one case or more widespread in the left parietotemporal region in three cases, but with a more pronounced reduction in the tem-



Technetium-99m HM-PAO single photon emission computed tomographic scans. Note the left-sided temporal hypoperfusion in patients 2 (top left), 3 (top right), 4 (bottom left), and 5 (bottom right), 18 months, 4 days, 1 day, and 4 days, respectively, after the transient global amnesic attack. Right side of patient is at left side of figure.

poral lobe. The absence of prior TIA, stroke, or asymptomatic infarcts on brain CT establishes a likely temporal relation between TGA and SPECT hypoperfusion. Performed 6 weeks after the amnesic attack, SPECT was normal in one patient. The hypothesis of an undetected transient hypoperfusion could be considered but remains uncertain. In four of our right-handed patients, the regional hypoperfusion involved the left dominant temporal region. In several reports of TGA,[4,9,10,13,15,36,43-45] the lateralization of the lesion was variable but similarly involved the dominant hemisphere in most cases.

The rare CBF studies in TGA have demonstrated a regional hypoperfusion in the temporal lobe, as in our patients. Stillhard et al[46] described one well-studied patient in whom HM-PAO SPECT examinations showed a transient bitemporal hypoperfusion during and after the amnesic episode. In a short report, Fayad et al[47] found, in two of the four patients in whom HM-PAO SPECT was performed within 24 hours after the episode, a moderate hypoperfusion in the left temporal lobe despite normal EEG and CT. The follow-up scans obtained in one patient were normal, yet clinical details and discussion are lacking. In another study,[45] using the xenon inhalation test, the regional CBF (rCBF) showed, in two patients, an overall decrease during the attack, with a more marked hypoperfusion in the temporal region. The rCBF was normal in two other cases 24 and 48 hours after the amnesic episode. In another report, Crowell et al[26] found, in five of the seven patients tested, an impaired vasomotor response in the watershed area between the middle cerebral artery and posterior cerebral artery territories, or a focal ischemia in the inferior part of the temporal lobe. These rCBF abnormalities differed from those seen in patients with vertebrobasilar TIAs.

Positron emission tomography (PET) has been studied in three patients with TGA.[48-50] During the amnesic episode, PET demonstrated overall decreases of rCBF, with a more marked hypoperfusion and hypometabolism (decreased regional cerebral oxygen metabolism, decreased regional oxygen extraction ratio) in the temporal region. Control PET was normal 24 hours after the amnesic attack. In another study,[51] PET showed better preserved rCBF and oxygen metabolism in four patients with TGA compared with seven patients with TIA in whom more marked focal reductions were observed.

Although the previous CBF studies have demonstrated transient circulatory disturbances, SPECT showed in our patients a persistent regional hypoperfusion when examinations took place 6 weeks (case 1), 3 months (control in case 4), or 18 months (case 2) after the amnesic attack. The origin of this chronic regional hypoperfusion remains unclear in the absence of associated neurologic deficits or CT-proved infarcts. In some series, brain CT showed infarction in the temporal lobe,[10,13,43] thalamus,[9,10,43] lentiform nucleus,[43,44] or parieto-occipital lobe.[4,10] In our patients, we hypothesize that chronic regional hypoperfusion could be due to "partial infarction"[52] or cortical diaschisis from small deep infarcts undetected on CT,[53-55] but these concepts remain uncertain. A regional hypometabolism with decreased rCBF has been reported in epileptic foci between attacks.[56,57] However, the lack of prior partial or generalized seizures, convulsion or unconsciousness during the ictus, or focal EEG abnormalities argues against epilepsy in our patients.

Many reports have found a high rate of stroke risk factors in TGA,[4,8,9,11,14] whereas others,[26,58-60] including a case-control study of 114 cases,[27] have not found a higher prevalence of such risk factors as compared with the normal population. In our patients, who had no history of migraine or epilepsy, the presence of cerebrovascular risk factors, mainly hypertension, supports a vascular mechanism. We therefore suggest that SPECT showing regional hypoperfusion could be useful to determine subgroups of patients with TGA due to a vascular mechanism, thus requiring further investigations for cerebrovascular risk factors and appropriate treatment. A high incidence of TIA and stroke further complicating TGA has been reported in small studies, mostly including patients with neurological deficits.[4,8,9,11,14,60] On the contrary, two large uncontrolled studies[58,59] and a case-control study[27] including patients with pure TGA showed a low incidence of stroke compared with that of a normal population or TIA control groups. During a follow-up period of 12 to 32 months, none of our patients with a regional hypoperfusion on SPECT and treated with aspirin suffered TIA, stroke, or recurrent TGA. Thus, in this small group of treated patients with a short follow-up, the presence of regional hypoperfusion on SPECT does not seem to have a predictive value for subsequent ischemic events, but further large studies with prolonged follow-ups would be needed.

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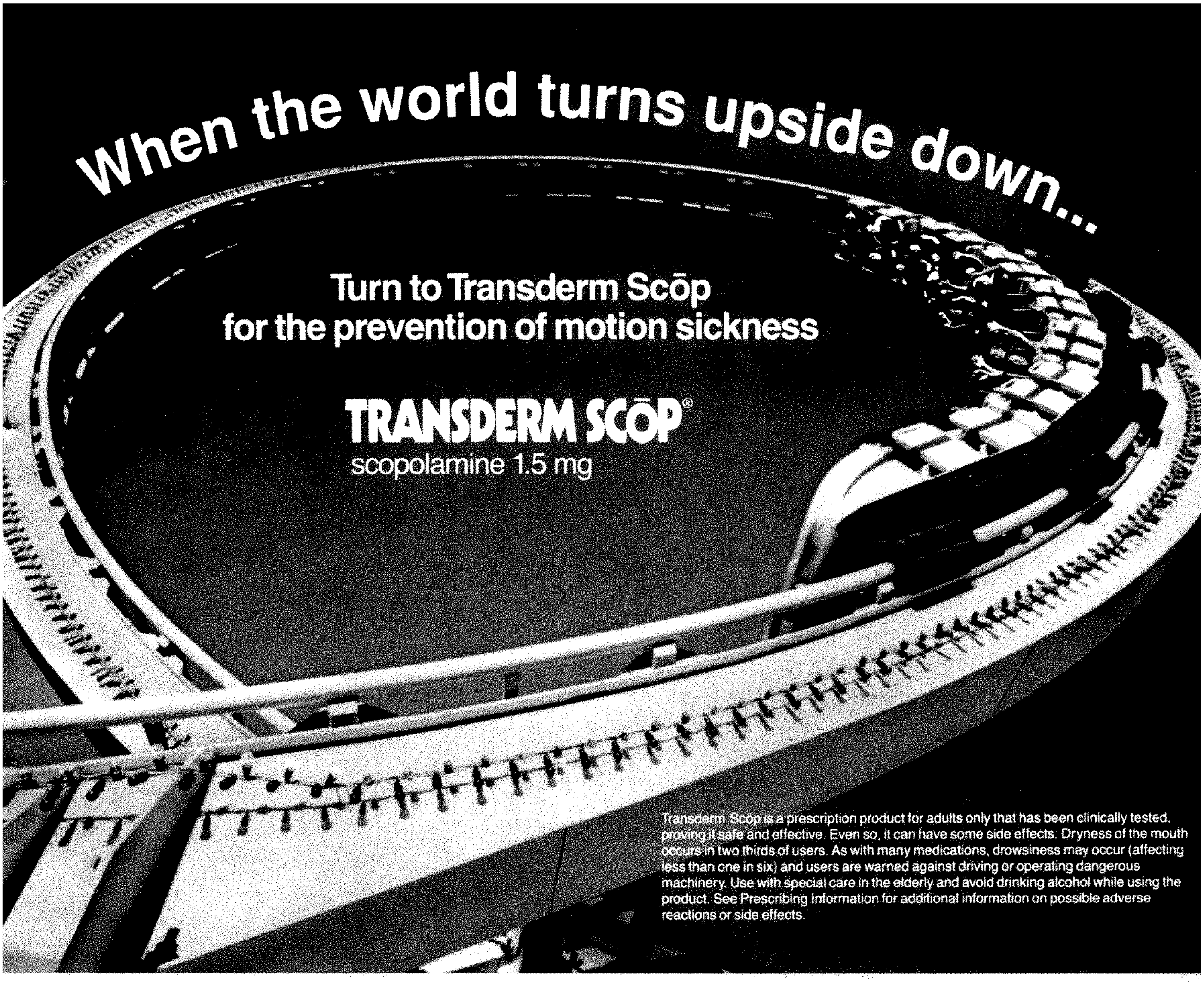
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Programmed delivery *in vivo* of 0.5 mg of scopolamine over 3 days

INDICATIONS AND USAGE

Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS

Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS

Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

***Handling:** After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION

Federal law prohibits dispensing without prescription.

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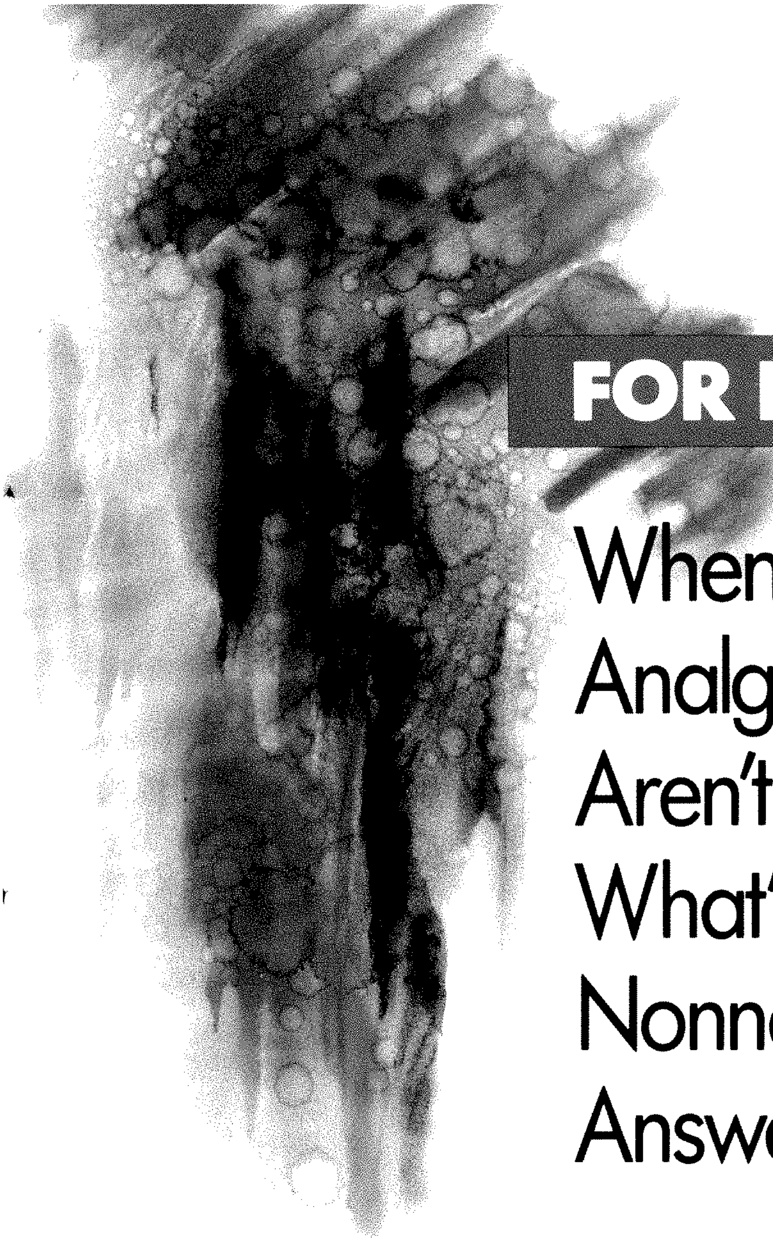

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ACTIONS

Dihydroergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels, and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to ergotamine, the adrenergic blocking actions are more pronounced, the vasoconstrictive actions somewhat less pronounced, and there is reduced incidence and degree of nausea and vomiting.

Onset of action occurs in 15 to 30 minutes following intramuscular administration and persists for 3-4 hours.

Repeated dosage at 1 hour intervals up to 3 hours may be required to obtain maximal effect.

INDICATIONS

As therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so-called "histaminic cephalalgia" when rapid control is desired or when other routes of administration are not feasible.

CONTRAINDICATIONS

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy. Hypersensitivity.

ADVERSE REACTIONS

Numbness and tingling of fingers and toes, muscle pains in the extremities, weakness in the legs, precordial distress and pain, transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged use of dihydroergotamine.

DHE-0192-01 1/92

DOSAGE AND ADMINISTRATION

For vascular headache, 1 mL intramuscularly at first warning sign of headache, repeated at 1 hour intervals to a total of 3 mL. Optimal results are obtained by titrating the dose for several headaches to find the minimal effective dose for each patient and this dose should then be employed at onset of subsequent attacks. Where more rapid effect is desired, the intravenous route may be employed to a maximum of 2 mL. Total weekly dosage should not exceed 6 mL.

OVERDOSAGE

Failure to observe the upper limits of repeated parenteral dosage may result in eventual ons of the peripheral toxic signs and symptoms of ergotism. Treatment includes discontinuance of t drug, warmth, vasodilators, and good nursing care to prevent tissue damage.

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As a clear, colorless and stable solution in ampuls containing:

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[NOVEMBER 15, 1990 DHE-Z20(BB)]

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Neuropsychological Correlates of White-Matter Lesions in Healthy Elderly Subjects

A Threshold Effect

*Kyle Brauer Boone, PhD; Bruce L. Miller, MD; Ira M. Lesser, MD; C. Mark Mehringer, MD;
Elizabeth Hill-Gutierrez, RN; Mark A. Goldberg, MD; Nancy G. Berman, PhD*

• The clinical significance of white-matter lesions (WMLs) detected by computed tomography and magnetic resonance imaging in healthy elderly subjects has been controversial, with some studies reporting associated deficits in cognition and others failing to document cognitive disturbance. In our sample of 100 healthy elderly individuals, almost half (n=46) had no WMLs, approximately one fourth had minimal (≤1 cm²; n=27) or moderate (>1 cm² but ≤10 cm²; n=21) WML areas, and six subjects had large WML areas (>10 cm²). Substantial disturbances in basic attention and selected frontal lobe skills were detected in the six subjects with the large WML areas. These findings suggest that a "threshold" of WML area must be present before cognitive deficits are observed. Surprisingly, no significant relationships between duration of hypertension or cholesterol levels and WMLs were detected, suggesting that factors other than vascular disturbances are involved in the origin of at least some WMLs.

(*Arch Neurol.* 1992;49:549-554)

Computed tomography (CT) and magnetic resonance imaging (MRI) in many healthy elderly individuals demonstrate white-matter "lesions" (WMLs). These lesions are seen as areas of lucency on CT scans and as areas of hyperintensity on MRI scans. In most healthy elderly subjects, these abnormalities involve a small volume of tissue, although in a minority of subjects the areas are large and confluent.[1] In some individuals, MRI white-matter hyperintense areas represent small infarcts; in other subjects, there is accumulation of fluid adjacent to hypertensive vessels, while in still others only white-matter pallor is detected.[2-4] For this reason, Hachinski et al[5] have coined the term *leukoaraiosis* (thinning of cerebal white matter) to describe these white-matter abnormalities. The clinical significance of these WMLs remains unclear, with some authors reporting that, in the elderly population, they are associated with neuropsychological deficits[6,7] and with others failing to document a relationship between the presence and severity of white-matter changes and cognitive abnormalities.[8-16]

The discrepancies in the published reports may stem from several sources. Differences in the neuropsychological tests employed and in the cognitive skills sampled have been substantial, with some investigators using simple screening tools and others employing more comprehensive test batteries. Also, the extent of WMLs has varied widely. It is also likely that in the studies in which CT was used, the lesions were larger compared with those identified in investigations employing MRI. Finally, small sample sizes and variations in age and exclusion criteria of the subject groups may have played a role in the differences in findings across reports.

The literature on cerebral diseases that involve primarily white matter suggests that subtle declines in specific frontal lobe/subcortical abilities should be expected. For example, patients with multiple sclerosis show declines in information processing speed and "frontal systems" abilities, such as conceptual reasoning, as well as memory difficulties.[17,18] Similarly, Wolfe et al[19] reported that patients with multiple lacunar infarcts primarily involving the basal ganglia, thalamus, and periventricular white matter showed an "apathetic" frontal syndrome characterized by perseverations and difficulties in shifting mental set, deficits in semantic clustering, decreased word list generation, and poor inhibition of habitual responses. Also, Kinkel et al[20] and Gupta et al[21] have argued for the presence of a "frontal system defect"/subcortical dementia characterized by slowness, poor concentration, blunting of affect and lack of spontaneity, and depressed learning rate and recall in their neurologic patient populations with WMLs.

In conclusion, while it appears that patients with WMLs associated with stroke or other neurologic conditions may show signs of a frontal syndrome and/or subcortical dementia, it is unclear (1) whether nonsymptomatic older

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adults with WMLs also will show subtle signs of subcortical or frontal dysfunction and (2) how extensive the WMLs must be in order for the cognitive decline to occur. Herein, we address these issues.

SUBJECTS AND METHODS

Subject Selection

One hundred subjects were recruited through an advertisement in the health sections of local newspapers requesting that elderly individuals were wanted for a study about normal aging. Informed consent for the evaluation procedures was obtained from each respondent. The volunteers were screened for psychiatric illness with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.*[22] To meet eligibility criteria, subjects had to be free of current or past psychotic, major affective, and alcohol and other drug dependence disorders; score 24 or greater on the Mini-Mental State Examination[23]; and speak English fluently. Also, subjects underwent physical and neurologic examinations, including a complete blood chemistry panel, complete blood cell count, and thyroid function panel. Subjects were excluded if there was a history or physical findings of neurologic disease, such as stroke, Parkinson's disease, or seizure disorder. Also excluded were individuals with laboratory findings showing serious metabolic abnormalities (eg, low sodium level, elevated glucose level, or thyroid or liver function abnormalities). Mean (±SD) age was 62.8±9.7 years (range, 45 to 83 years), mean educational level was 14.2±2.8 years, and mean Full-Scale IQ (FSIQ) was 113.9±14.8. Sixty-four subjects were female and 36 were male. There were 80 white, 10 black, six Hispanic, and four Oriental subjects. Twenty-one of the subjects had histories of current and/or past hypertension.

Magnetic Resonance Imaging

An MRI scanner with a 1.5-T superconducting magnet (Picker International, Cleveland, Ohio) was utilized, and scanning was performed in multiple planes. Axial scanning was performed along the canthomeatal line from the skull base to the vertex in 10-mm sections. A repetition time of 2000 milliseconds was employed, and echo times of 20 and 100 milliseconds were used to provide more T_1- and T_2-weighted scans. Coronal plane images were obtained through the entire brain at 10-mm intervals. All scans were obtained with two repetitions to maintain image quality.

The scans were transferred to magnetic tape, and specific measurements were made at a viewing console. A cursor controlled by a joystick was used by one of us (C.M.M.) to outline the periphery of any region of interest. Area was automatically calculated (to 0.01 cm^2) once the region was delineated.

White-matter lesions were defined as poorly demarcated, patchy areas in the white matter, separate from the ventricles, that appeared as areas of hyperintensity. No subject had definite evidence of white-matter infarction, defined as well-demarcated, wedge-shaped areas that followed a specific vascular territory and/or extended to the cortex. All T2-weighted axial sections were examined for lesions; the area of WMLs on each section was summed to provide an overall estimate of white-matter disease. Coronal images were used to corroborate and better define the location of abnormalities.

Neuropsychological Test Battery

A battery of neuropsychological tests was administered and included the Wechsler Adult Intelligence Scale–Revised (WAIS-R; Satz-Mogel Format),[24,25] Wechsler Memory Scale (WMS)[26] or Wechsler Memory Scale–Revised (WMS-R)[27] Logical Memory (LM) and Visual Reproduction (VR) subtests, Rey-Osterrieth Complex Figure (RO),[28] Wisconsin Card Sorting Test (WCST),[29] Stroop Test,[30] Auditory Consonant Trigrams (ACT),[31,32] and Verbal Fluency (FAS).[28] These measures provided information regarding frontal lobe function (WCST, Stroop 3, and ACT), general intelligence (WAIS-R), memory (LM and VR subtests), attention and information processing speed (WAIS-R, Digit Span [DS] and Digit Symbol [DSym], and Stroop 1 and 2), language (FAS), and visuospatial skills (RO).

The test variables used for analysis included number of categories (WCST cat) and perseverative responses (WCST pers) on the WCST; time (in seconds) to complete the word reading, color naming, and color-interference section of the Stroop test; total score on the ACT; total number of words generated for the letters *f*, *a*, and *s* on the FAS; raw scores for the DS and DSym subtests of the WAIS-R; total score for copy of the RO; and the percentage of retention on 45-minute delay for the LM and VR subtests of the WMS and 30-minute delay for the LM and VR subtests of the WMS-R. The WMS LM subtest was scored according to Schear's[33] criteria, and the WMS VR subtest was scored according to the WMS Manual and Trahan's[34] guidelines. The WCST was scored by a computer[35] to circumvent questions regarding interrater reliability.

RESULTS

Data analysis focused on the identification of relationships between the neuropsychological test results and total WML area (defined as the summed individual lesions). Almost half of the subjects (n = 46) had no WMLs, and approximately one fourth (n = 27) had minimal WML areas (≤1 cm^2). Another quarter (n = 21) of the sample had moderate WML areas (>1 cm^2 but ≤10 cm^2), while six subjects had large total areas of WMLs (>10 cm^2). The Table shows the means and SDs for demographic and neuropsychological variables for the four groups. Analysis of variance comparisons revealed significant differences in age ($P = .0001$) and selected neuropsychological scores tapping "frontal lobe" abilities (ACT: $P = .001$; WCST cat: $P = .045$; WCST pers: $P = .009$; and Stroop 3: $P = .004$), attention (DS: $P = .004$), and speed of information processing (DSym: $P = .002$; Stroop 2: $P = .04$). To examine further the performance on DS, the groups were compared on DS forward and backward scores. Significant group differences were obtained on these additional measures (DS forward: $P = .007$; DS backward: $P = .04$). Pair-wise *t* tests adjusted for multiple comparisons (Bonferroni correction) indicated that the group differences were attributable to poorer performance in the subjects with WML area greater than 10 cm^2.

No significant differences were documented in education, Mini-Mental State Examination score, FSIQ or measures of verbal and nonverbal memory (LM and VR subtests), visuospatial ability (RO), or language (FAS). In the assessment of memory, subjects were either administered the original WMS or its recent revision, the WMS-R. It was unclear whether use of these two formats might have obscured any group differences on the statistical comparisons. Approximately three fourths of the sample was administered the original WMS (n = 77), while the remainder was given the WMS-R (n = 23). The *t* test comparisons indicated that the percent retention scores for LM were comparable across forms (WMS LM: 79.16±16.89; WMS-R LM: 78.32±15.89), while percent retention scores for VR were significantly lower in those subjects completing the original WMS (WMS VR: 59.12±24.94; WMS-R VR: 74.04±26.60). The use of two VR formats apparently differing in level of difficulty does not appear to have sabotaged the detection of significant group differences on the VR measures. Of the six subjects with large WMLs, all but one was administered the original WMS VR, and all of these individuals scored well

Means (±SDs) for Demographic and Neuropsychological Variables Across White-Matter Lesion (WML) Groups*

Variable	WML Area 0 cm² (n=46)	≤1 cm² (n=27)	>1 to ≤10 cm² (n=21)	>10 cm² (n=6)	P
Age	58.2±8.5	63.6±9.9	69.2±6.8	72.0±4.9	.001
Education	14.2±2.8	15.0±1.9	14.2±3.1	12.8±1.3	.25
MMSE	29.5±0.8	29.4±0.9	29.1±1.3	29.5±0.8	.38
FSIQ	113.9±14.8	114.4±11.0	113.5±16.3	105.2±10.0	.52
DS	11.3±2.3	11.0±2.3	11.1±2.3	8.5±2.1	.02
Forward	8.7±2.1	8.6±1.9	8.1±2.0	5.7±1.9	.0067
Backward	7.5±2.3	6.7±1.7	6.9±1.5	5.3±1.2	.22†
ACT	46.0±7.7	46.6±6.8	47.6±6.4	33.7±11.1	.001
WCST categories	4.4±1.8	5.2±1.5	4.5±2.1	2.8±2.3	.045
WCST perseverative responses	24.6±24.4	19.0±16.0	24.0±25.9	57.5±45.8	.0086
Stroop test 1	42.9±7.8	44.6±6.2	44.2±7.1	50.5±12.1	.14
Stroop test 2	59.0±8.6	63.2±11.1	64.3±15.8	71.3±7.9	.47†
Stroop test 3	120.4±30.0	134.8 ± 27.4	142.0±40.7	171.0±69.7	.11†
DSym	53.8±9.7	49.2±12.3	44.0±12.8	40.0±8.8	.36†
FAS	42.2±10.8	40.7±11.4	39.1±11.7	30.7±8.3	.11
RO copy	33.7±2.4	32.7±4.4	31.4±5.1	33.3±1.0	.13
WMS LM %	78.9±17.5	80.7±13.4	78.5±18.3	72.5±20.0	.77
WMS VR %	66.9±22.6	59.8±27.6	57.6±30.5	58.8±27.4	.40

*MMSE indicates Mini-Mental State Examination; FSIQ, Full-Scale IQ; DS, Digit Span; ACT, Auditory Consonant Trigrams; WCST, Wisconsin Card Sorting Test; DSym, Digit Symbol; FAS, Verbal Fluency; RO, Rey-Osterrieth Complex Figure; WMS, Wechsler Memory Scale; LM, logical memory; and VR, visual reproduction.

†After covarying for age.

within 1 SD of the mean of the 77 subjects completing the WMS. In fact, four of the five scored at or above the group mean. The one subject with a large WML area who was administered the WMS-R VR scored between 1 and 2 SDs below the mean of the 23 subjects completing the WMS-R.

Age correlated significantly with performance on four of the 15 neuropsychological variables after controlling for the number of correlations computed (DSym: $r = .48$; Stroop 2: $r = .34$; Stroop 3: $r = .33$; and DS backward: $r = .27$). We were concerned that the significant group differences obtained on these measures might have been due to the age differences across groups. When these four group comparisons were recalculated controlling for age with analysis of covariance, the group differences were no longer significant.

To control for the inflation in type I error associated with the multiple comparisons, the test variables were divided into "families" composed of similar cognitive skills, with the .05 significance level divided by the number of "members" in each family.[36] Specifically, the three DS scores were evaluated as a group, with a resultant P value of .017, and the four "frontal" test scores (WCST cat, WCST pers, ACT, and Stroop 3) were examined as a group, with a resultant P value of .013. (The rest of the test variables, such as the memory and information processing speed scores, were not grouped, because no significant group differences were detected for any of them with a P value of .05.) With the use of this technique of grouping by families, two of the three comparisons of DS scores were significant (DS total and DS forward), and two of four group differences on frontal lobe tasks remained significant (ACT and WCST pers). With a more stringent multistage Bonferroni procedure[37] that controlled for type I error for all 13 primary group comparisons on neuropsychological measures, the group differences on ACT and DS remained significant. Most important, the significant group differences followed a consistent pattern[38] rather than being distributed randomly across the various neuropsychological measures. Specifically, the test results supported the hypothesis of an association between WMLs and frontal and subcortical cognitive dysfunction; significant group differences were found on frontal lobe measures and attentional tasks but not on any of the memory, FSIQ, language, visuospatial, or information processing speed tests.

The six subjects with the most WMLs had affected areas of 11.3, 11.4, 11.8, 15.9, 16.4, and 32.8 cm². In all subjects, the lesions were scattered within frontal, parietal, and occipital lobes. Specifically, five of these six subjects exhibited lesions adjacent to the occipital horns and centrum semiovale bilaterally, and four subjects demonstrated lesions in the corona radiata and subcortical white matter of both frontal and parietal lobes bilaterally. Less commonly, lesions were found in the occipital lobes not adjacent to the ventricles, the right parietal lobe adjacent to the body of the lateral ventricle posteriorly, the left frontal area near the frontal horn, forceps major bilaterally near the occipital horn, and forceps minor of both frontal lobes.

Although we had predicted that patients with large confluent WMLs would do more poorly on tests of frontal lobe function, the initial classification of subjects into

WML groupings had been done somewhat arbitrarily, and the question arose as to whether the six subjects with WML area greater than 10 cm^2 were a homogeneous group in terms of neuropsychological performance. Examination of the neuropsychological test scores for each of these six individuals indicated that on most tests, the subjects performed similarly. However, for ACT, FAS, and FSIQ, the three patients with the most WMLs scored substantially worse than the three patients with WML area greater than 10 cm^2 and less than 12 cm^2. Specifically, for ACT, the mean score for the three subjects with WML areas greater than 12 cm^2 was 26.0 (vs 41.3 for the three subjects with WML areas less than 12 cm^2). Similarly, for FAS, the group with WML areas greater than 12 cm^2 obtained a mean of 24.0 words (vs 37.3 in the group with WML areas less than 12 cm^2). The FSIQ score was 96.7 in the group with WML areas greater than 12 cm^2 (vs 113.7 in the group with WML areas less than 12 cm^2).

Four of the six subjects with large WMLs had a history of current and/or past hypertension, while only 18% (17/94) of the remaining subjects had such a history. However, the correlation between WMLs and duration of hypertension for the group as a whole failed to reach statistical significance—a history of high blood pressure accounted for less than 5% of the variance in WMLs ($r = .22$). Similarly, no significant relationships were found between cholesterol measures and WMLs ($r = .10$).

No subjects had evidence of a cortical infarct or definite lacunar infarctions. However, seven subjects showed evidence of small basal ganglia gray-matter areas of intensity that ranged from 0.05 to 0.2 cm^2. These subjects were represented in all of our WML size groupings: one subject had no WMLs, one had a small area of WMLs (0.3 cm^2), four had a moderate area of WMLs (1.3 to 2.3 cm^2), and one had a large area of WMLs (16.4 cm^2).

COMMENT

Our data show that when the area of MRI-detected WMLs surpassed 10 cm^2, subtle disturbances were noted in basic attention and selected frontal lobe functions. In the six subjects with a lesion area greater than 10 cm^2, the lesions tended to be large and confluent, involving multiple brain areas. White-matter lesions of this size were found in 6% of healthy elderly subjects stringently screened for medical and psychiatric abnormalities. Our subjects with a WML area greater than 10 cm^2 performed more poorly than subjects with smaller areas of WMLs on tasks that assessed forward digit span and "divided" attention (remembering letters while subtracting by threes). Also, they made more perseverative responses and completed fewer categories on a sorting task. The mean scores of the subjects with the largest areas of WMLs on these variables were at least 1 SD below the mean performance of the group as a whole (clinically significant). No significant declines in IQ, memory, language, or visuospatial skills were documented, and, after controlling for age, no differences in speed of information processing were found.

Our findings regarding WMLs identified with MRI are based on, to our knowledge, the largest sample of healthy elderly subjects studied to date and represent the first report of a relationship between cognitive decline and MRI-detected WMLs in an older nonpatient sample. The only other publications to document an association between cognition and WMLs in such a population employed CT.[7,8] In the sole study that utilized both CT and MRI data, Kobari and colleagues[7] found a relationship between cognitive scores and CT-detected WMLs but not between cognition and MRI-detected WMLs. Awad et al[39] reported that CT scans are only able to detect WMLs that are severe on MRI scans. Thus, the available data would suggest that cognitive declines occur only with relatively large WMLs, which, with our quantitative system, corresponds to areas of WMLs greater than 10 cm^2 on MRI scans.

Our findings of cognitive decline associated with WMLs in an elderly population are in agreement with those of the work of Steingart and colleagues[6] but would appear to be at variance with findings reported by Austrom et al,[8] Bernardin et al,[9] Fein et al,[10] Hendrie et al,[12] Hunt et al,[13] Rao et al,[14] Brant-Zawadzki et al,[15] and Schmidt et al,[16] all of whom generally failed to find any association between neuropsychological scores and WMLs in young or older nonneurologic populations. However, these various reports considered in conjunction with our results reveal a fairly consistent pattern of the selective effects of WMLs on cognition. Specifically, the majority of the studies[8-10,12-16] included tests of IQ, visual and verbal memory, reaction time, word generation, information processing speed, and/or overall cognitive functioning (eg, dementia screening examinations) and, consonant with our data, found no association between WMLs and these cognitive scores.

Tests of "frontal lobe" function only were included in the studies conducted by Hunt et al,[13] Bernardin et al,[9] and Rao et al.[14] Hunt et al administered motor sequencing tasks thought to be associated with frontal lobe functioning and found no relationship between WMLs and test performance after age was controlled for. However, this study involved a small number of subjects with severe WMLs ($n = 4$), and the small sample size may have made it difficult to detect significant relationships between WMLs and test scores. Alternatively, frontal motor tasks may not be sensitive to the cognitive decline associated with WMLs.

Bernardin et al[9] and Rao and colleagues[14] assessed their subjects with a comprehensive battery of neuropsychological tests, including tests of frontal lobe function (eg, WCST, ACT, and Stroop). They did obtain some significant group differences but concluded that these were chance associations due to the multiple comparisons. However, in the report by Rao et al, one of the three significant group differences occurred on a Brown-Peterson (or Consonant Trigrams) measure, a finding that concurs with those reported herein. Similarly, in the report by Bernardin et al, hypertensive subjects with WMLs performed more poorly than hypertensive subjects without WMLs on some of the Brown-Peterson (Consonant Trigrams) measures and on the number of perseverative errors on the WCST as well as on some memory test measures. The sample sizes of both studies were small (only 10 and 17 subjects, respectively, had WMLs), which may partially account for the lack of additional significant group differences. Also, in the study by Rao et al, WMLs were rated for presence but not severity. It is possible that the WMLs in the 10 affected subjects were generally too small to cause cognitive decline. In the report by Bernardin et al, severity was rated according to a three-point scale, and most subjects had small lesions (<5 mm), and more than half had only one or two lesions. In a subset of three subjects with extensive lesions, deficits were noted in "attention, memory, and abstract reasoning," and the subject with the most extensive lesions showed declines in "verbal fluency, cognitive processing speed, and motor speed, and excessive perseverative tendencies, disinhibition, and inappropriate behavior," findings that are similar to ours. Bernardin et al and Rao et al concluded that a "threshold" extent of WMLs may be necessary before neuropsychological impairment is seen.

The only prominent discrepancy that emerged across reports was the failure of other investigators who administered the Digit Span subtest of the WAIS-R[9,10,14,15] to document the decline in basic attention that we observed in our sample. However, while Fein et al[10] concluded that test/retest data on their two subjects showed no cognitive decline, digit span performance was actually consistently lower than performance on other WAIS-R subtests. In all the studies to date, the number of subjects with WMLs has been very small (range, two to 17), which may have contributed to the failure to document significant findings. Whether declines in basic attention are a replicable characteristic of WMLs awaits further confirmation.

The mild decline in basic and "divided" attention and categorization skills as well as increased perseverative behavior could be consistent with the early stages of a subcortical dementia/frontal system defect. Disturbances in these cognitive areas have commonly been found to be associated with frontal cortical or subcortical dysfunction.[31,32,40] Our subjects with a large area of WMLs clearly do not meet criteria for a dementia and do not show declines in all the cognitive skills commonly found in a subcortical dementia/frontal systems defect, such as in memory, information processing speed, and word generation. It is possible that the mild disturbance in attention and increased perseverations may represent the frontal and/or subcortical skills most susceptible to disruption and those that decline first as a result of WMLs.

In the six subjects with a large area of WMLs, the lesions were located in frontal, parietal, and occipital lobes. It might be argued that to produce a "frontal lobe" syndrome, the lesions should be clustered anteriorly. However, Mesulam[41] suggested that a frontal lobe syndrome would be expected with the presence of "multifocal partial lesions (none of which are individually severe enough to disrupt specific cognitive domains such as language or memory)," which collectively sabotage the integration by the frontal lobes of networks for complex behavior.

Our sample of six subjects with an area of WMLs greater than 10 cm^2 is too small to allow us to describe with any confidence the types and sequence of cognitive declines that occur with areas of WMLs that are progressively larger than 10 cm^2. However, these six subjects tended to fall into two groups, with three of the subjects having WML areas of 11 to 12 cm^2 and the remainder having WML areas greater than 15 cm^2. On three neuropsychological variables (FSIQ, FAS, and ACT), the three subjects with the larger WML areas consistently performed more poorly than the other three subjects. It is possible that in subjects in whom the WML area exceeds 15 cm^2, significant deterioration in global intellectual functioning and word generation may emerge, as well as further declines in divided attention. This would be consistent with evidence that more than 95% of patients with multi-infarct dementia have large WML areas (mean area, 26.7 cm^2).[42] As we continue to enlarge our sample size, we will be able to provide answers to these questions as well as to the relationship between specific location of WMLs and cognition.

Several authors have hypothesized that declines in frontal lobe abilities are common in healthy elderly subjects and may in fact reflect the core cognitive abilities lost with age.[43-45] However, in a previous publication,[46] we failed to document much evidence of decline in frontal lobe abilities in a sample of medically and psychiatrically healthy elderly individuals that excluded subjects with MRI abnormalities, including a WML area of 5 cm^2 or greater. It is possible that the other reports of frontal decline with age were due to inclusion of subjects with undetected cerebral abnormalities, including a large WML area.

Our sample was limited to individuals aged 45 years and older, and the association documented between cognition and WMLs may be unique to older individuals. The causes of WMLs may differ in old vs young subjects,[14] and this may differentially affect the associated cognitive profile.

Despite the hypothesized relationship between age-related WMLs and cerebrovascular risk factors,[5,47,48] we did not document statistically significant associations between WMLs and hypertension or cholesterol measures. Apparently, factors other than hypertension, diabetes, or elevated serum cholesterol level must play a role in the origin of at least some WMLs. Future studies need to explore the relationship of episodic hypotension, cerebral amyloidangiopathy, and potential nutritional factors in the pathogenesis of WMLs in the elderly.

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Original Contribution

Malignant Tumors in the Pituitary Gland

Patrick Juneau, MD; William C. Schoene, MD; Peter Black, MD, PhD

• Malignant tumors of the pituitary gland may mimic pituitary adenomas both in clinical presentation and in imaging, and often present with neurologic findings including visual field loss and extraocular movement palsies. We describe a 58-year-old woman without known malignancy who presented with extraocular movement weakness, loss of facial sensation, and a sellar plasmacytoma; a 49-year-old woman with oculomotor palsy, no known malignancy, and rapidly failing vision who had metastatic lung carcinoma; and a 70-year-old woman with metastatic breast carcinoma who presented with rapidly failing vision and a metastasis to the anterior lobe of the pituitary. These cases illustrate several important features of malignancy in the pituitary fossa: that it can mimic a "nonfunctioning" pituitary adenoma in clinical presentation and imaging; that rapidly progressive visual loss, extraocular movement palsies, or facial sensory loss may help to distinguish it from a benign adenoma; and that when the pathologist evaluates an alleged "nonsecretory" or "nonfunctional" adenoma, metastases should be included in the differential diagnosis.

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Malignant tumors of the pituitary gland are uncommon but important sellar lesions. They may mimic "nonfunctioning" pituitary adenomas, but they have a higher incidence of associated visual loss, diplopia, panhypopituitarism, and diabetes insipidus.[1,2] They should be considered in the differential diagnosis of diplopia or visual loss in patients with or without known carcinoma. We describe three patients we operated on between January and December of 1990 who illustrate the clinical presentation of metastatic carcinoma to the pituitary. These cases represent 8% of the transsphenoidal procedures performed for endocrine inactive pituitary tumors during that period.

Based on clinical data, the diagnosis of sellar malignancy was entertained preoperatively in each case. Magnetic resonance imaging (MRI) did not by itself lead to a distinctive preoperative diagnosis. The neurologist should be aware of pituitary metastases and may see them more often as neuroimaging is performed routinely on patients with systemic malignancy.

REPORT OF CASES

CASE 1.—A 58-year-old white woman with no history of malignancy presented with a 3-month history of diplopia, progressive headache, and numbness over the right side of her face. No clinical or laboratory evidence of endocrinopathy was apparent. On examination, she had a right abducens palsy, a slightly diminished corneal reflex, and slightly decreased sensation over all three divisions of the right trigeminal nerve. No visual field loss was noted.

Magnetic resonance imaging with gadolineum revealed an expanded sella with an enhancing sellar mass and suprasellar extension with marked extension into the sphenoid sinus (Fig 1). The suprasellar component extended anteriorly to the orbital apex and posteriorly to the pons, and clival destruction was present. The tumor appeared to involve the cavernous sinus, encasing the carotid arteries. A diagnosis of malignant tumor was made preoperatively.

In the operating room, the patient underwent microsurgical transsphenoidal debulking of the mass. The lesion was extremely vascular, and the surgeon's impression was that it was a malignant tumor; the initial pathologic diagnosis was a pituitary adenoma.

The postoperative course was uneventful and the patient's symptoms initially resolved. When the patient's facial numbness returned within 6 months of surgery, however, review of the slides and further staining for immunoproteins led to the recognition that this tumor was a plasmacytoma. With radiation therapy, her symptoms again resolved and the mass disappeared. She received 4000 cGy to the whole brain and meningeal fields and appeared stable 12 months after irradiation.

CASE 2.—A 49-year-old white female smoker with no history of malignancy presented with a 5-month history of headaches and a 9-kg weight loss. Over the preceding 2 months, she had noticed failing vision in both eyes, worse on the right, which progressed rapidly the week before surgery. On examination she had complete loss of light perception in the right eye, accompanied by an ipsilateral oculomotor nerve palsy. A complete temporal visual field cut was noted in the left eye, and visual acuity was markedly decreased to 20/400.

Magnetic resonance imaging with gadolineum revealed an enhancing mass filling the sella with substantial suprasellar extension (Fig 2). Compression of the optic nerves and chiasm was considerable, and the tumor appeared to invade the cavernous sinus. The preoperative diagnosis of malignancy was based on clinical and imaging data. The patient's preoperative chest roentgenogram showed a left midlung density interpreted as possibly being confluence of vascular structures, scar, or tumor.

The patient was taken to the operating room for decompression of the visual apparatus using a transsphenoidal technique. Tumor invaded the diaphragm sellae, and complete resection led to a marked cerebrospinal fluid leak. This was successfully stopped with fascia and fat packing of the sphenoid sinus as well

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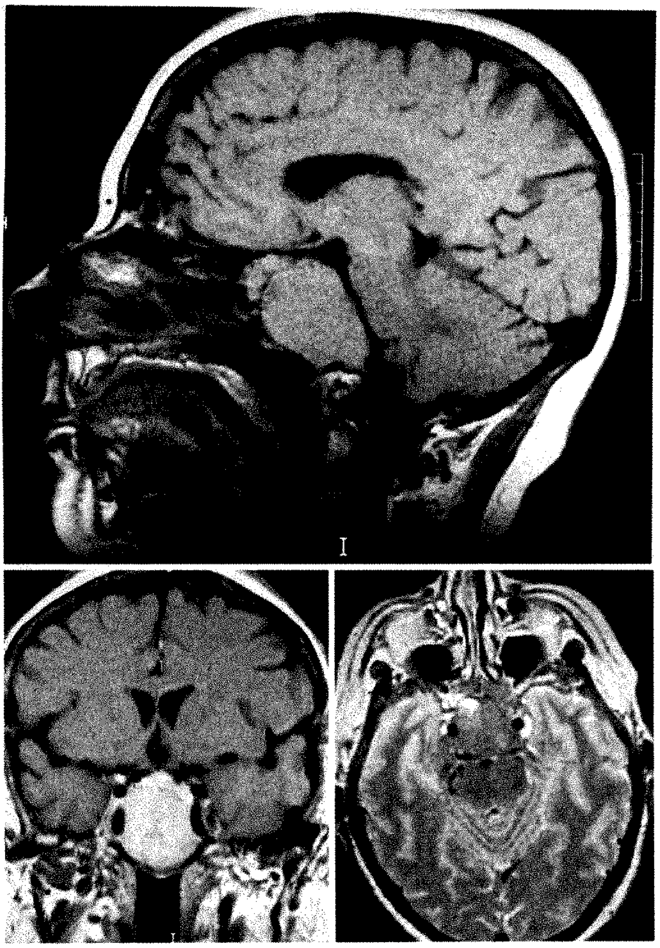

Fig 1.—*Case 1. Sagittal (top), coronal (bottom left), and transaxial (bottom right) views of a patient with a plasmacytoma. The tumor fills the sphenoid sinus (top), has virtually destroyed the clivus (bottom left), and extends into the cavernous sinus (bottom right).*

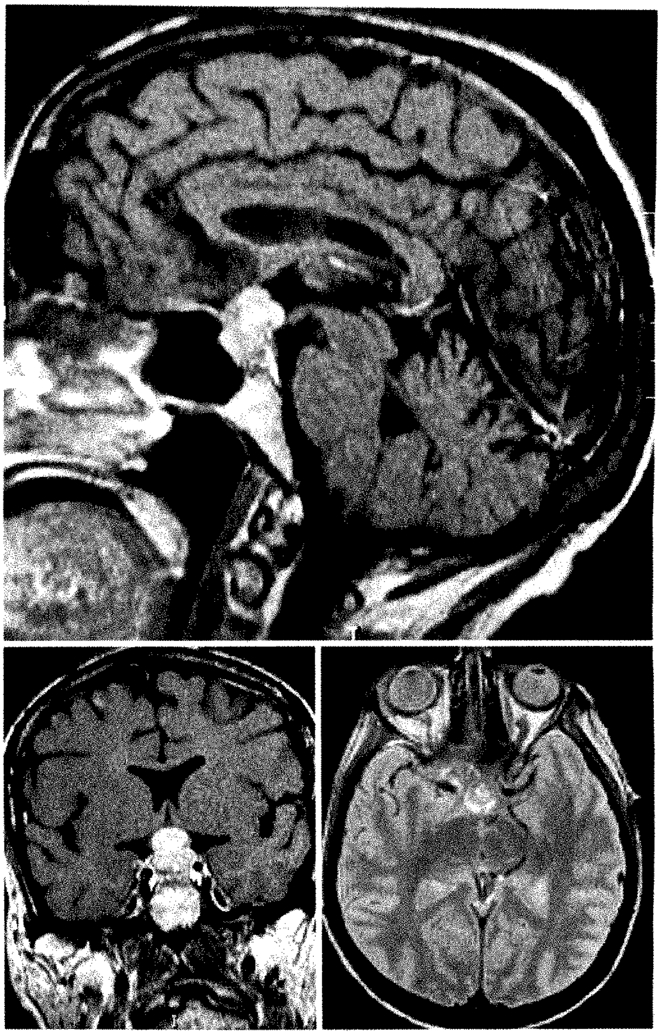

Fig 2.—*Case 2. Magnetic resonance imaging scans of a patient with metastatic bronchogenic carcinoma to the sella turcica. The tumor spills out of the sella into the suprasellar space (top, sagittal view); the waisting created by the diaphragm sellae can be seen on the coronal plane (bottom left). Bottom right shows a transaxial view.*

as the sella. The pathologic diagnosis was metastatic adenocarcinoma to the anterior pituitary.

Postoperatively the patient developed transient diabetes insipidus. Her vision had improved within 2 weeks of surgery and returned to normal in the left eye and to 20/100 in the right eye within 1 month of surgery. Metastatic workup confirmed a hilar mass on a computed tomographic scan of the chest. A biopsy specimen of the mass revealed a bronchogenic carcinoma. The patient subsequently underwent irradiation of the whole brain and chest. She remained clinically stable 9 months after resection.

CASE 3.—A 70-year-old white woman with previously diagnosed and treated metastatic breast carcinoma presented to the neurosurgical service with a several-week history of failing vision and headaches. She had had an adenocarcinoma of the breast discovered 3 years before, leading to a right radical mastectomy, and at presentation had two skin deposits of tumor in the left temporal area but was otherwise without known metastatic disease. Her skin lesions began to resolve with chemotherapy. She also had a long history of cardiac disease with a porcine aortic valve. No clinical or laboratory evidence of endocrinopathy was noted preoperatively. Her ophthalmologic evaluation revealed a complete bitemporal hemianopia and diminished visual acuity with no extraocular movement weakness.

Magnetic resonance imaging with gadolineum revealed an expanded sella with an enhancing sellar mass and considerable suprasellar extension (Fig 3).

The patient was taken to the operating room for urgent decompression of the optic nerves and chiasm with a transsphenoidal approach. At surgery the sella was enlarged and the floor was thin. Very firm tissue with a homogeneous fibrous character filled the sella; this was very difficult to curette, and rongeurs had to be used to achieve adequate decompression. The diaphragm sella was tightly adherent to the tumor mass, making a cerebrospinal fluid leak a necessary part of adequate resection; the leak was repaired by packing both the sella and the sphenoid sinus. Laterally it was possible to dissect tumor off the cavernous sinus dura without excessive bleeding. Posterior pituitary tissue was not identified; the anterior lobe was thinned and pushed posteriorly in the sella. The pathologic diagnosis was metastatic adenocarcinoma to the anterior pituitary.

Postoperatively the patient had improvement in her visual fields to full perimetry with normal acuity, and her headaches were cured. She began postoperative irradiation of the pituitary through temporal portals. Her suprasellar lesion completely resolved; however, 8 months after surgery she developed a clival lesion ventral to the medulla outside the previous portals, which required further radiation therapy.

COMMENT

Malignant deposits in the pituitary gland have received increasing attention recently[1-3]; they can occur not only in the normal gland but also in pituitary adenomas.[4,5] The incidence of metastatic tumors in surgical series varies:

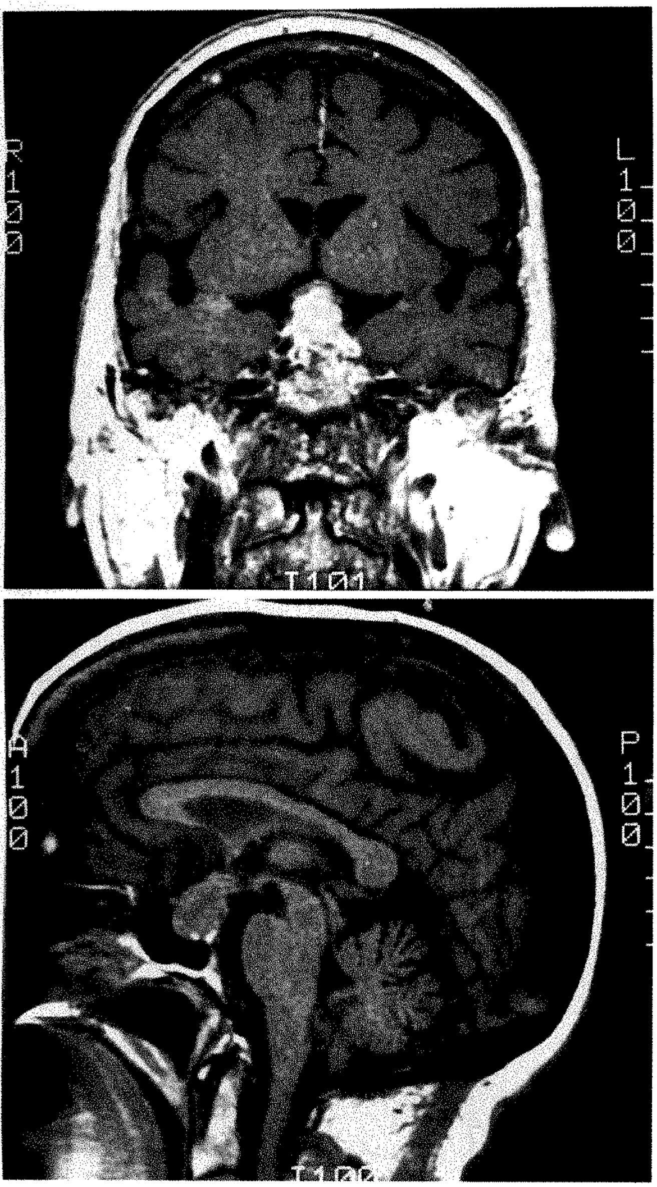

Fig 3.—*Case 3. Magnetic resonance imaging scans of a patient with metastatic adenocarcinoma of the lung. The tumor pushes well above the diaphragm and into the sphenoid sinus and has an irregular contour. Top, coronal view. Bottom, sagittal view.*

Branch and Laws[2] found them to represent 1% of all pituitary masses; and McCormick et al,[1] 8%; we calculated that they represented approximately 8% of endocrinologically silent adenomas.

The two cases of metastatic tumor represent typical sources of metastatic carcinoma to the pituitary gland, the breast, and the lung. Approximately 50% of all pituitary metastases are from the breast, and pituitary metastases occur in 5.3% to 14.9% of all patients with metastatic breast carcinoma.[6,7] McCormick et al[1] reviewed 220 cases, including autopsy cases, from the literature. They demonstrated the breast as a source in 49.8%; lung in 20.2%; gastrointestinal tract in 6.4%; prostate in 6%; melanoma in 2.3%; and leukemia, pharynx, endometrium, pancreas, thyroid, paranasal sinus, cervix, multiple myeloma, germ cell, larynx, liver, ovary, penis, and kidney in less than 2%. Most patients were between 50 and 80 years of age, usually dying of advanced systemic disease before symptoms referable to the pituitary became apparent. Most of the tumors described before computed tomography and MRI had wide use had been discovered incidentally either at autopsy or at hypophysectomy for pain control in patients with metastatic breast carcinoma.[7,8]

Patients with multiple myeloma masquerading as a pituitary tumor have also been described.[9,10] One was a 65-year-old man with sudden diplopia and paresis of the third and fourth cranial nerves[10]; another was a 51-year-old man with diabetes insipidus and an enlarged sella turcica.[9]

Presentation

Data from autopsies suggest that most pituitary metastases are asymptomatic in patients who have widespread carcinoma.[6,7,11,12] The older literature emphasized diabetes insipidus as a sign of pituitary metastasis in patients with symptoms.[13,14] McCormick et al[1] reviewed 40 cases published before 1987 and found that 70% of the patients presented with diabetes insipidus, 20% with visual field loss, 12% with extraocular movement palsies, and 15% with hypopituitarism. This may, however, reflect a time before computed tomographic scanning, when tumors were considerably more advanced before they were detected. Recent surgical reports suggest that visual field loss, extraocular movement weakness, and hypopituitarism are just as prominent as presenting findings. Among 14 patients, Branch and Laws[2] found headache in 65%, anterior hypopituitarism in 64%, visual field loss in 50%, extraocular movement weakness in 43%, and diabetes insipidus in only 28%. They suggested that the triad of headache, extraocular movement weakness, and diabetes insipidus strongly suggests metastasis. Of three patients described by Duvall and Cullen,[15] two presented with field loss and one with third-nerve palsy; Cox's[16] patient had asymptomatic bitemporal hemianopia;and Nelson and colleagues'[17] patient had ophthalmoplegia and ptosis. Thus, the presentation may be subtle and involve a combination of visual system and pituitary signs.

Imaging

Our MRI data suggest, and other authors have also indicated,[1,2] that preoperative imaging may not be helpful in distinguishing metastatic tumor from pituitary adenoma. McCormick et al[1] and Branch and Laws[2] reported that computed tomography is not particularly helpful in establishing that a lesion is a metastasis. McCormick and colleagues suggested that skull roentgenograms showing sclerotic margins to an enlarged sella or aggressive bony destruction imply metastatic disease. Two of their four patients underwent MRI, and their conclusions were the same as ours concerning the specificity of this test: the MRI is not characteristic in metastatic disease.[1] Metastatic tumors may erode the sella and extend laterally and above the sella, just as adenomas do. Nothing about their MRI appearance allows the preoperative diagnosis to be made with confidence; in a patient without known metastatic disease this can be a problem, as the initial pathologic diagnosis may not be accurate.

Pathology

Pathologic diagnosis may be difficult, and metastatic carcinoma must be included in the differential diagnosis of a nonfunctioning pituitary adenoma. McCormick et al[1] noted a renal carcinoma that had initially been read as a pituitary adenoma, and in our first case, multiple myeloma was initially thought to be a pituitary adenoma. Although early reports suggest that metastases go to the posterior rather than the anterior lobe,[18] there are many cases now documented with anterior lobe hypofunction as the major finding. Leramo et al[19] found hypopituitarism and hyperprolactinemia without diabetes insipidus in their case.

Surgery

It is our impression that metastatic pituitary lesions are more difficult to deal with surgically than the usual adenomas. They are firm and bloody, making curetting difficult; they are attached to surrounding structures, making it difficult to resect them without disturbing the diaphragm sellae; and they are often large and invasive enough to make complete removal problematic.

Radiation Therapy

In most series radiation therapy has been used; the problem of whether to irradiate the entire head or just the parasellar region is one that has to be considered carefully. Of some potential concern is the possibility of subarachnoid spread with penetration of the diaphragm sellae, making ongoing surveillance for meningeal carcinomatosis important. In one of our cases, irradiation of the parasellar region was later accompanied by clivus recurrence, suggesting that whole-head radiation therapy is appropriate.

CONCLUSIONS

In summary, metastatic tumors to the pituitary can be the first presentation of an occult malignancy and may present with visual loss, extraocular movement palsy, or hypopituitarism. Improved neuroimaging, especially MRI, may allow earlier detection of these lesions but does not definitively distinguish them from pituitary adenomas.

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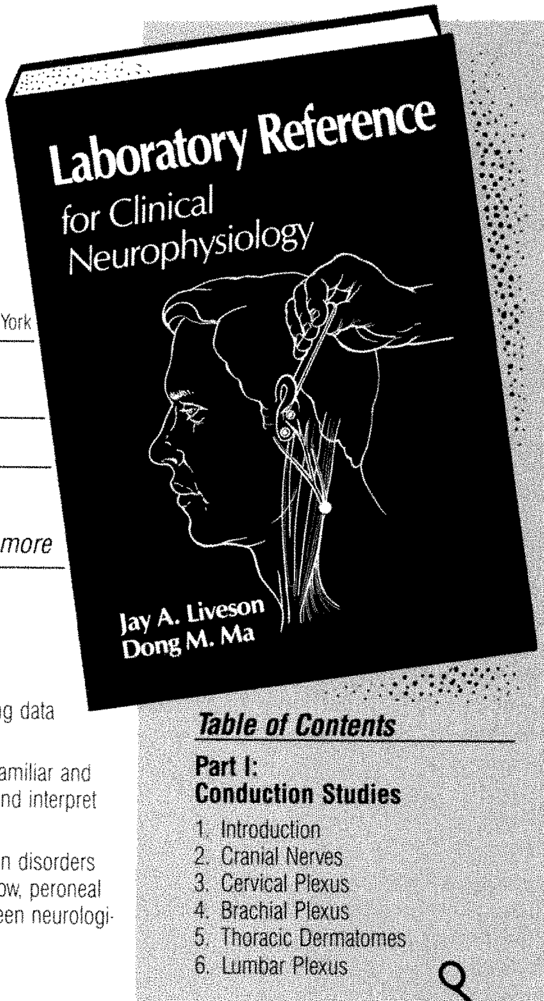

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Dopamine Agonist Treatment of Fluctuating Parkinsonism

D-2 (Controlled-Release MK-458) vs Combined D-1 and D-2 (Pergolide)

J. Eric Ahlskog, PhD, MD; Manfred D. Muenter, MD; Patricia A. Bailey, RN; Patricia M. Stevens, RN

• Adjunctive treatment with the very potent and selective dopamine D-2 agonist MK-458 (controlled-release formulation) improved the control of parkinsonism in patients with fluctuating responses to levodopa therapy (with carbidopa). We subsequently switched patients to adjunctive treatment with pergolide, a less potent D-2 agonist. Pergolide therapy controlled parkinsonism more effectively than controlled-release MK-458. Unlike MK-458, pergolide mesylate also has D-1 agonist properties, apparently accounting for its greater antiparkinsonism efficacy. Adjunctive treatment with controlled-release MK-458 elicited less choreiform dyskinesias than either pergolide adjunctive therapy or therapy with carbidopa-levodopa alone; this finding suggests that D-1 receptor stimulation contributes to the elicitation of medication-induced chorea. The highest doses of controlled-release MK-458 resulted in paradoxical freezing of gait in almost one third of patients. This finding suggests that gait freezing, common in untreated parkinsonism, can also be elicited by excessive D-2 stimulation.

(*Arch Neurol.* 1992;49:560-568)

Levodopatherapy often produces fluctuating, short-duration responses, in addition to dyskinesias, as Parkinson's disease persists beyond a few years. The short-duration responses to therapy with levodopa probably reflect a progressive reduction of dopaminergic nigrostriatal terminals, with diminished capacity to concentrate and decarboxylate levodopa and provide a storage pool of dopamine.[1-5] Clinical investigations have focused on direct-acting dopamine agonists as a means of countering these complications with levodopa because these drugs bypass the presynaptic terminal.

The D-2 subclass of dopamine receptors has been thought to be the primary mediator of the antiparkinsonian response to dopamine-agonist medications.[6,7] Perhaps the prototypic D-2 agonist drug is MK-458 ([+]-4-propyl-9-hydroxynaphthoxazine; PHNO), which is not only selective[8-15] but also one of the most potent D-2 agonists yet identified by in vivo testing in animal models.[8,9] Preliminary studies have suggested that MK-458 does benefit patients with fluctuating parkinsonism when used as adjunctive therapy with carbidopa-levodopa, despite the fact that the doses employed in these studies have not been increased to the maximum.[16,17]

These favorable preliminary results with MK-458 were the impetus for the initial phase of this investigation, in which controlled-release MK-458 was administered in a 6-month trial to patients with Parkinson's disease who were experiencing carbidopa-levodopa–related clinical fluctuations and dyskinesias. Considerably higher MK-458 doses were employed than in previous studies, and this drug was formulated with a hydroxypropylmethylcellulose/lactose (HPMC) matrix; prior studies have suggested that controlled-release MK-458 has a similar potency but longer duration of action than the standard formulation.[18] The dose of carbidopa-levodopa was reduced as necessary, whereas that of MK-458 (HPMC) was increased. Efficacy was measured near the end of the 6-month study and compared with the baseline responses to therapy with carbidopa-levodopa alone.

After completion of the 6-month study, treatment with MK-458 (HPMC) was tapered, and patients were then given pergolide mesylate; ultimately, this approach allowed a comparison of these two dopamine-agonist medications. Whereas MK-458 is a pure D-2 agonist, devoid of D-1 activity,[8,9,11-15] pergolide is a combined D-1 and D-2 agonist[19-22] but a less potent D-2 agonist than MK-458 in vivo.[8-10] Recently, it has been recognized that stimulation of the D-1 subclass of dopamine receptors contributes to the motor responses to levodopa and direct dopamine agonists[23-34]; indeed, synergism between D-1 and D-2 receptors has been demonstrated.[26-32,35]

SUBJECTS AND METHODS

MK-458 (HPMC) Substitution Study

Subjects.—All 24 patients who entered the study (17 men and seven women) had idiopathic Parkinson's disease with short-duration responses to therapy with carbidopa-levodopa and clinical fluctuations. Their mean age was 63 years (range, 41 to 76 years), mean duration of Parkinson's disease was 8.3 years

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(range, 1 to 19 years), and mean duration of levodopa therapy was 6.8 years (range, 1 to 15 years). The Hoehn and Yahr[36] stages ranged from 1 to 4 (mean, 2.8; median, 3.0). All patients were receiving a stable dose of carbidopa-levodopa for at least 1 month before entry into the study. The four patients who were taking amantadine hydrochloride and the seven patients who were taking anticholinergic drugs or diphenhydramine hydrochloride continued to take these medications throughout the study. All patients signed an informed consent after the details of the study had been fully explained at the time of enrollment. Patients with unstable medical conditions apart from parkinsonism were excluded by a baseline general medical history and physical examination, blood tests (complete blood cell count and chemistry profile), urinalysis, electrocardiogram, and chest roentgenogram.

Study Design.—Controlled-release MK-458 was administered orally twice a day; it was formulated with an HPMC matrix, as previously tested.[18] The starting dose was 1.5 mg/d, with slow upward titration during the first 3 months of the 6-month study up to as high as 30 mg twice per day. As the dose was slowly increased, the dose of carbidopa-levodopa was reduced as necessary, guided by the clinical response. During the last 3 months of the study, we attempted to maintain stable doses of all the antiparkinsonian medications. After initiation of MK-458 (HPMC) therapy, patients returned for office visits eight times during the course of the 24-week study.

A standardized battery of efficacy measures was performed twice before MK-458 (HPMC) therapy was initiated and twice near the end of the study. The two baseline measures were obtained 2 weeks and again 1 day before initiating MK-458 (HPMC) therapy, while the patients were receiving stable doses of carbidopa-levodopa. The end-of-study efficacy measures were determined at 20 and 24 weeks after initiation of MK-458 (HPMC) therapy.

The efficacy measures included medication-response temporal profiles, in which the patients' responses to the medications were serially scored over a 335-minute test period. These were begun between 7 and 10 AM, before the patients received their first dose of medications for the day. Four measures of motor function were used for these profiles. First, the motor examination battery from the Unified Rating Scale for Parkinsonism[37] was scored, with the motor examination items (numbers 18 through 31) weighted for better representation of the contribution to function (maximum parkinsonian severity score, 31). Second, dyskinesia was scored with an unweighted scale (0 to 4) for each of the four limbs, the trunk, and the head/neck; the total possible dyskinesia score was 24. Third, patients were scored on a standardized walking test, recording the time required to rise from a chair, walk 20 ft, return, and sit down. Fourth, key-tapping speed was assessed with patients alternately depressing each of two counters (mounted 20.3 cm apart) as rapidly as they could for 60 seconds. Each hand was individually scored and then the two scores were added. Practice effects were minimized by 2 minutes of warm-up time on the key-tapping device at the beginning of the test day plus 10 seconds of warm-up before each scored trial.

All four of these motor response measures were scored 35 minutes before and again 5 minutes before the antiparkinsonian medications were administered. These measures were repeated at 30, 60, 90, 120, 150, 180, 240, and 300 minutes after drug administration. To control for and assess the effects of meals on the drug responses, we provided each patient with a high-protein breakfast between the 90- and 120-minute assessments during one of the two baseline profiles and also during one of the end-of-study profiles. The other two medication-response profiles were performed entirely in the fasting state. Half the patients underwent the fasting profile first and half last (the order in each phase of the study was independently randomized). Patients arrived for these medication-response profiles in the fasting state.

Patients also filled out diary cards for 4 days during the baseline period and again near the end of the study; they recorded whether they were "on," "on with dyskinesia," "off," or "asleep" for every half hour during a 24-hour cycle. Patients also tallied the number of times they switched "off" per 24 hours. The Northwestern University Disability Scale[37] provided a measure of activities of daily living; this was scored twice during the baseline period and twice near the end of the study, and each pair of scores was averaged. Global evaluations of the responses to the study drug were rated by both the patient and the physician (J.E.A. or M.D.M.) with a standardized seven-grade scoring system ("markedly worse" to "markedly improved"). We tabulated the adverse events on the basis of the patients' reports and the end-of-study general physical examination findings and laboratory test results (blood tests, urinalysis, and stool examination for occult blood were performed five times during the study; electrocardiography was performed four times, and chest roentgenography was performed once at the end of the study).

Transition to Pergolide

All patients were discontinued MK-458 (HPMC) therapy after 6 months and the dose was tapered to zero over 2 weeks. The carbidopa-levodopa dose was concomitantly raised toward the prestudy dose, guided by the clinical response. All patients who completed the 6-month MK-458 (HPMC) protocol were offered transition to substitution therapy with open-label pergolide mesylate. Patients who chose to enter this phase of the study were started on a dose of 0.05 mg/d of pergolide mesylate in addition to their current dose of carbidopa-levodopa. The pergolide dose was slowly increased during a period of several weeks on a regimen of three times daily, up to what was thought to be each patient's optimal dose (maximum dose, 7 mg/d). As the dose of pergolide was slowly increased, that of carbidopa-levodopa was concomitantly reduced, if indicated by the clinical response. Once it was concluded that the pergolide and carbidopa-levodopa adjustments had been optimized, the dosage of both medications was kept constant. The efficacy measures described for the MK-458 (HPMC) study were repeated when the patients had been receiving stable doses of pergolide and carbidopa-levodopa for at least 1 week and had been receiving pergolide for a total of 3 to 6 months. Adverse events with the use of pergolide were also recorded. Patients who had been receiving anticholinergic drugs, diphenhydramine, or amantadine during the first phase of the study continued to take stable doses of these medications through this open-label pergolide phase.

Statistical Analysis

Planned statistical comparisons were performed with the use of paired t tests, except when the assumptions for parametric tests could not be met, in which case the Wilcoxon Signed-Rank Test or Sign Test was used. Categorical variables were analyzed with χ^2 analysis (Fisher's Exact Test). $P<.05$ (two-tailed test) was considered statistically significant.

RESULTS

MK-458 (HPMC) Substitution Study

Of the 24 patients who entered the study, 22 tolerated MK-458 (HPMC) and completed the 6-month trial. One patient dropped out after 1 month because of a single syncopal episode possibly related to the study drug. A second patient completed the study but was unable to tolerate more than minimal doses of MK-458 (HPMC) because of nausea, vomiting, and somnolence. This patient was not taking MK-458 (HPMC) during the last week of the study, and her data are not included in the analysis of the efficacy measures.

The 22 patients who completed the study were able to reduce their total daily dose of levodopa by almost 30% (Table 1). Despite this, the carbidopa-levodopa dosing frequency changed only slightly (Table 1).

Prolonged monitoring of the motor responses to single-medication doses was performed twice during the pre-

Table 1.—Daily Doses of Medications in 22 Patients With Parkinson's Disease During the Substitution Study With MK-458 (HPMC)*

Medications	At Baseline (Entry)	Near End of Trial	P†
Mean total daily dose, mg/d (range)			
Levodopa	1185 (300-2700)	853 (150-1800)	.0002
Carbidopa	200 (40-437)	144 (15-313)	.0001
MK-458 (HPMC)	. . .	37 (12-60)	. . .
No. of doses per day of carbidopa-levodopa	7.5 (3-10)	7.2 (4-10)	NS†

*Four patients continued to take amantadine, and six patients continued to take anticholinergic drugs throughout the study.
†NS indicates not significant.

study phase (results were averaged) and compared with the two averaged end-of-study motor response profiles when the patients were receiving stable doses of MK-458 (HPMC). The mean Unified Rating Scale for Parkinsonism motor examination scores are shown in Fig 1, top. Patients receiving a single dose of both MK-458 (HPMC) and carbidopa-levodopa had significantly improved mean motor scores 2.5 hours after taking medications and thereafter compared with the scores after single doses of carbidopa-levodopa alone ($P<.05$). There was also a statistically significant difference ($P<.05$) between the areas under the two Parkinson motor score curves shown in Fig 1, top. The mean carbidopa (19 mg)-levodopa (124 mg) dose administered for the end-of-study profiles was substantially lower than the mean dose for the baseline assessments (173 mg). The mean interval from the last nighttime dose of carbidopa-levodopa before the profiles to the time of medication administration for the motor response profiles was almost identical during the baseline assessments (11.7 hours) as the end-of-study assessments (11.3 hours). The mean dose of MK-458 (HPMC) used for the end-of-study motor response profiles was 18.9 mg.

Patients tended to have less dyskinesia while taking MK-458 (HPMC) and carbidopa-levodopa than when taking carbidopa-levodopa alone, as demonstrated during the medication-response profiles (Fig 1, bottom). The mean dyskinesia score at the time of peak effect, 60 minutes after medications, was significantly ($P<.05$) lower with adjunctive MK-458 (HPMC) therapy. However, the difference in areas under the two dyskinesia curves shown in Fig 1, bottom, was not statistically significant.

Medication-response profiles from two patients with the greatest recorded improvement are shown in Fig 2. The high-protein meal had no substantial effect on the subsequent motor scores. Perusal of all of the individual patients' medication-response profiles failed to reveal any substantial meal effects; hence, the effect of meals on the motor scores was not analyzed further.

Finger-tapping speed improved after the addition of MK-458 (HPMC). The medication-response profiles revealed an especially pronounced benefit beginning 2 hours after medication doses (Fig 3, top). The difference in the area under the two tapping score curves shown in Fig 3, top, was just short of reaching statistical significance ($P=.0510$).

Serial timed walking test scores tended to improve with the addition of MK-458 (HPMC), as shown in Fig 3, bottom; however, there were no statistically significant differences between the values before and after use of MK-458 (HPMC), nor was the area under the two curves significantly different.

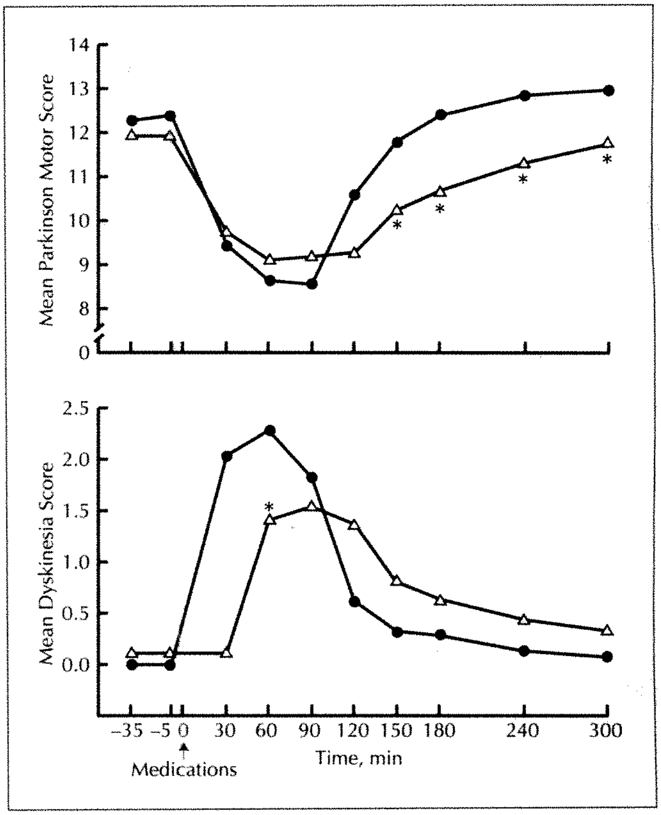

Fig 1.—*Top, Parkinson motor scores. Serial scoring of Unified Rating Scale for Parkinsonism (examination items 18 through 31, weighted) following single doses of medications. The average of two prestudy drug-response profiles obtained on separate days (employing carbidopa-levodopa alone) were compared with the average of two end-of-study profiles (employing MK-458 [hydroxypropylmethylcellulose/lactose or HPMC] plus carbidopa-levodopa). Bottom, Dyskinesias. Asterisks indicate* $P<.05$ *for prestudy vs end-of-study values. Circles indicate carbidopa-levodopa alone; triangles, MK-458 (HPMC) plus carbidopa-levodopa.*

More than 80% of patients rated themselves "improved" on the global rating scale; physicians' ratings were similar (Table 2). Patient-scored diary card data revealed significantly less dyskinesia during the "on" states (Fig 4). There was also a slight trend toward less "off" time, but this did not reach statistical significance. Patients also tallied the number of times they switched "off" per 24 hours; this improved from the prestudy value of 4.9 to 3.4 at the end of the study ($P<.01$).

Activities of daily living were rated by the patients using the Northwestern University Disability Scale (normal, 0; most severe impairment, 50). The mean baseline score

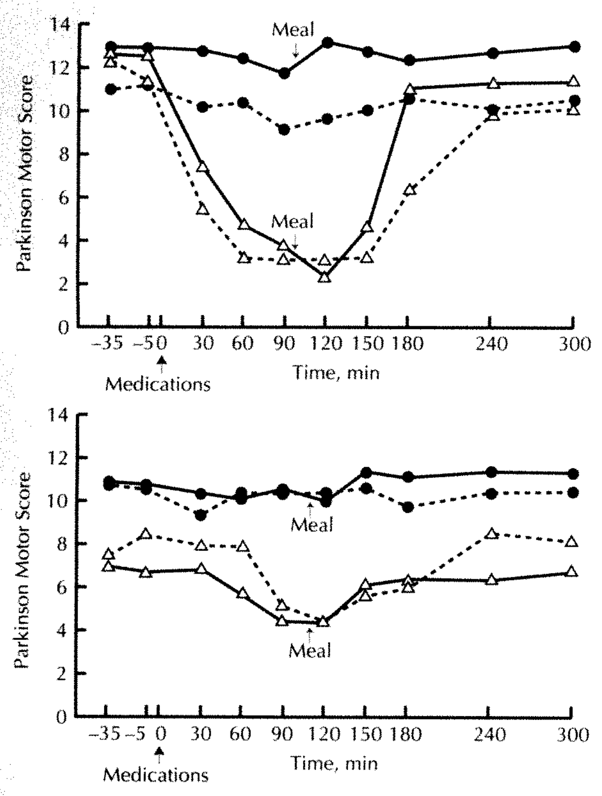

Fig 2.—*Drug-response profiles from two patients with the greatest recorded improvement with MK-458 (hydroxypropylmethylcellulose/lactose or HPMC). The medication-response profiles were performed twice during the prestudy phase (carbidopa-levodopa alone) and twice while patients were receiving adjunctive treatment with MK-458 (HPMC). The patient whose course is recorded on the bottom graph had improved scores before the first morning doses of the medications; this finding suggests that benefit from the study drug persisted overnight. Circles indicate carbidopa-levodopa alone; triangles, MK-458 (HPMC) plus carbidopa-levodopa. Top, Prestudy dose of carbidopa (25 mg)-levodopa (100 mg); end-of-study doses of carbidopa (25 mg)-levodopa (100 mg) and MK-458 (HPMC) (12 mg). Bottom, Prestudy dose of carbidopa (17.5 mg)-levodopa (175 mg); end-of-study doses of carbidopa (15 mg)-levodopa (150 mg) and MK-458 (HPMC) (18 mg).*

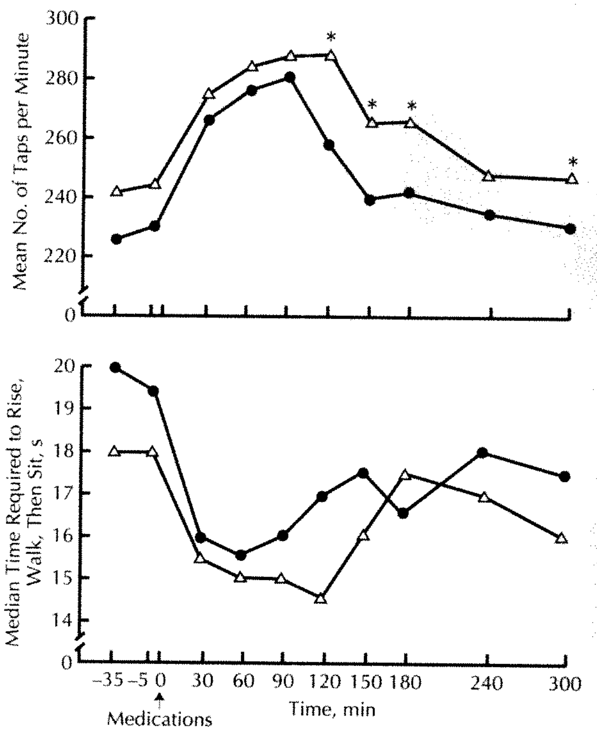

Fig 3.—*Top, Tapping. Numbers of taps alternating on two digital counters in 1 minute were recorded separately for each hand and then summed. The two prestudy response profiles (carbidopa-levodopa alone) were averaged and compared with the two averaged response profiles for adjunctive therapy with MK-458 (hydroxypropylmethylcellulose/lactose or HPMC). Asterisks indicate* P<.05. *Bottom, Rise, walk, then sit test. Serial measurements of the time required to rise from a chair, walk 20 feet, return, and sit were recorded. Median scores on the two prestudy evaluations were compared with median end-of-study scores (no statistically significant differences). Circles indicate carbidopa-levodopa alone; triangles, MK-458 (HPMC) plus carbidopa-levodopa.*

of 11.6 improved slightly to 10.4 with the use of MK-458 (HPMC); this difference was statistically significant ($P<.05$).

A common side effect encountered with the highest doses of MK-458 (HPMC) was freezing of gait. Paradoxically, this occurred at the time of peak medication effect. It resolved with reduction of the dosage of MK-458 (HPMC). This was noted in almost one third of our patients (Table 3). Other common adverse events included somnolence and nausea; various other side effects occurred less frequently (Table 3).

The patients' response to MK-458 (HPMC) plateaued before reaching the maximal dosage of 60 mg/d (Fig 5). Thirteen of 22 patients believed that their parkinsonism was less well controlled while receiving the highest doses of MK-458 and ultimately settled on a less-than-maximal dosage. This group included the seven patients experiencing gait freezing with the highest dosage. The maximal daily dosage of MK-458 allowed (60 mg) was being taken by seven patients at the end of the study; the data from these seven patients revealed plateaued responses that were very similar to those shown in Fig 5 for the entire group. Nonmotor side effects prevented maximal dose escalation in only two of the 22 patients.

Transition to Pergolide

All patients were discontinued MK-458 (HPMC) therapy after 6 months (2-week taper). Twenty patients elected to participate in the comparison open-label trial with pergolide. Pergolide mesylate therapy was not initiated until the patients had returned to what was believed to be their baseline state after discontinuation of MK-458 (HPMC) therapy. Despite the fact that pergolide was started in a low dose of 0.05 mg/d and only very slowly increased, five of the 20 patients who entered this phase of the study dropped out because of side effects. One patient who dropped out because of pergolide-elicited somnolence had also been intolerant of MK-458 (HPMC) because of nausea, vomiting, and somnolence in the previous phase of this study. Two patients dropped out of the pergolide phase because of chest pain, and the other two patients dropped out because of insomnia and

Table 2.—Global Evaluations of MK-458 (HPMC) Adjunctive Therapy in 22 Patients With Parkinson's Disease Compared With Carbidopa-Levodopa Therapy Alone

	Rating Scale, No. of Patients				
			Improvement		
Rater	Worse	No Change	Slight	Moderate	Marked
Patient*	4	0	4	10	4
Physician*	3	0	6	10	3

*Number improved vs number not improved: $P<.01$.

Table 3.—Adverse Events* in 24 Patients With Parkinson's Disease Who Were Taking MK-458 (HPMC)

Event†	No. of Patients
Paradoxical freezing of gait	7
Somnolence	6 (moderate to severe, n = 2)
Nausea	10 (severe, n = 4)
Insomnia	3
Headache	3
Confusion	3
Hypomania	2
Hallucinations	2
Dizziness, nonorthostatic	2
Syncope/presyncope	2
Diaphoresis	2
Abdominal discomfort	2
Hypertension	2
Joint pain	2
Ankle edema	2
Diarrhea	2
Low back pain	2

*Dyskinesias were excluded.

†One patient each had positive Hemoquant results, tinnitus, bradycardia, hypotension, urinary urgency, telangiectasia, weight loss, anorexia, chest-wall pain, rash, increased thirst, anemia, elevated creatine phosphokinase value, abnormal results of liver function tests, hypothyroidism, and hypokalemia. One patient died. This patient's condition markedly deteriorated after MK-458 (HPMC) therapy was tapered following completion of the study. Therapy was gradually restarted on a compassionate basis, but the patient died within a few days (autopsy revealed a cardiac cause of death). Two patients dropped out of the study due to syncope in one and nausea, vomiting, and somnolence in the other.

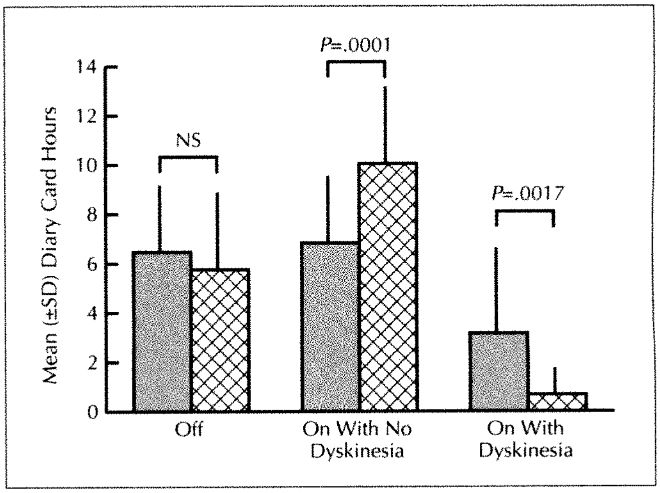

Fig 4.—*Comparison of diary card data. Patients recorded whether they were "on," "on with dyskinesia," "off," or asleep for every half hour during 4 baseline days while receiving carbidopa/levodopa alone (shaded bars) and for another 4 days near the end of the study while taking MK-458 (hydroxypropylmethylcellulose/lactose [HPMC]) plus carbidopa/levodopa (cross-hatched bars). NS indicates not significant.*

palpitations in one and nausea, vomiting, and syncope in the other.

The pergolide dosage was slowly increased to what was believed to be the optimum for each patient, and the dosage of carbidopa-levodopa was concomitantly reduced, guided by the clinical response, similar to the strategy used in the MK-458 (HPMC) trial. After stabilization, the total daily dose of levodopa in the pergolide trial was similar to that in the MK-458 trial, as was the dose of carbidopa (Table 4).

Patients served as their own controls, and the medication-response temporal profiles were compared in the three different conditions: carbidopa-levodopa alone, MK-458 (HPMC) plus carbidopa-levodopa, and pergolide plus carbidopa-levodopa. The scores of the two separate baseline medication profiles were averaged, as were the two MK-458 (HPMC) medication-response profiles, for comparison with the single pergolide temporal-response profile.

The mean levodopa dose of 145 mg used for the pergolide temporal-response profiles was almost identical to the mean dose of 132 mg used for the MK-458 (HPMC) profiles ($P=.4231$). The time of the last dose of carbidopa-levodopa administered before the medication-response profiles was recorded. The mean interval between that dose and the test dose administered for the medication-response profiles was almost identical during the pergolide trial (11.2 hours) to that during the MK-458 (HPMC) trial (11.7 hours) ($P=.2217$).

The medication-response profiles revealed improved performance with pergolide compared with MK-458 (HPMC). Pergolide therapy significantly improved the mean Unified Rating Scale for Parkinsonism motor scores at the time of peak response, 60 and 120 minutes after medication doses (Fig 6, top). The area under the pergolide curve shown in Fig 6, top, was significantly different ($P<.05$) from the area under the MK-458 (HPMC) curve, comparing data following medication administration.

The mean dyskinesia scores at the time of peak medication effect during the medication-response profiles were significantly greater with pergolide than with MK-458 (HPMC) (Fig 6, bottom). The area under the pergolide

Table 4.—Daily Doses of Medications in the Comparison Study of Pergolide and MK-458 (HPMC) in 15 Patients With Parkinson's Disease

Medication	At Baseline	MK-458 (HPMC) Trial	Pergolide Trial	MK-458 (HPMC) Trial vs Pergolide Trial, P*
Mean total daily dose, mg/d (range)				
Levodopa	1243 (600-2250)	908† (300-1650)	953† (350-1650)	NS (P=.61)
Carbidopa	217 (75-438)	158† (40-313)	155† (60-338)	NS (P=.82)
MK-458 (HPMC)	...	39 (12-60)	...	...
Pergolide	...	...	3.7 (1.5-7)	...
No. of doses per day of carbidopa-levodopa	7.8 (3-10)	7.3‡ (4-10)	8.0‡ (4-14)	NS (P=.15)

*NS, not significant.
†Significantly different ($P \leq .01$) from baseline value.
‡Not significantly different from baseline value.

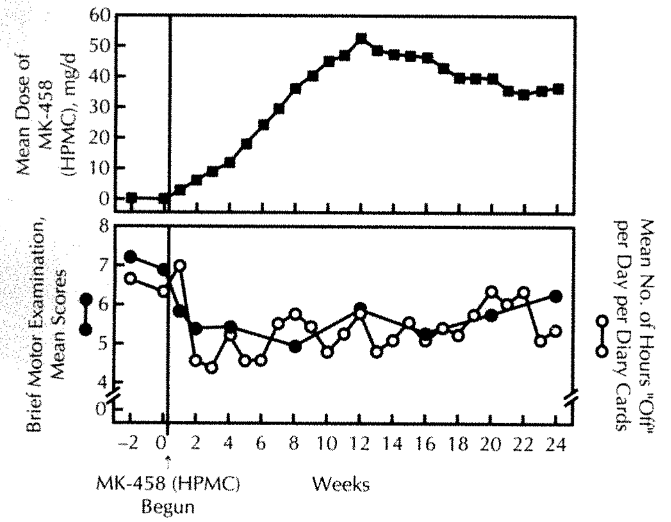

Fig 5.—*Motor response to MK-458 (hydroxypropylmethylcellulose/lactose [HPMC]) therapy. Response plateaued before the maximal allowed dosage of 60 mg/d was reached. The brief motor examination was a shortened version of the Parkinson motor examination described in the "Subjects and Methods" section. It consisted of weighted scores for rigidity, tremor, bradykinesia, gait, and postural stability. Analysis of the weekly Northwestern University Disability Scale scores showed similar plateauing of the benefit before the maximal dose of MK-458 was reached (not shown).*

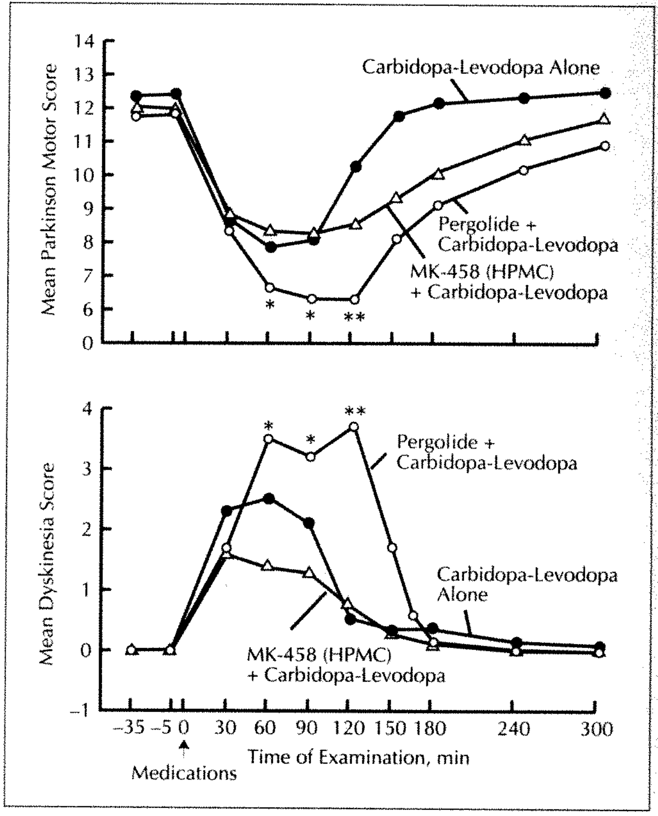

Fig 6.—*Fifteen patients underwent all three phases of this investigation and were assessed while receiving carbidopa-levodopa alone, then carbidopa-levodopa plus MK-458 (hydroxypropylmethylcellulose/lactose [HPMC]), and finally carbidopa-levodopa plus pergolide. Single doses of medications were administered for these response profiles after patients went without medications overnight. Pergolide vs MK-458 (HPMC) data points: single asterisk indicates P<.05; double asterisk, P<.01. Top, Parkinson motor scores on weighted Unified Rating Scale for Parkinsonism motor examination. Bottom, Dyskinesias (mean scores on the dyskinesia scale).*

dyskinesia curve (Fig 6, bottom) was significantly greater than the area under the MK-458 (HPMC) curve ($P<.01$).

The timed tapping test also revealed greater improvement with pergolide than with MK-458 (HPMC) (Fig 7, top). The area under the pergolide tapping curve shown in Fig 7, top, was significantly greater than the area under the MK-458 (HPMC) curve ($P<.02$). The median timed walking test scores with pergolide were not significantly different from those with MK-458 (HPMC) (Fig 7, bottom). The areas under the pergolide and MK-458 (HPMC) timed walking curves shown in Fig 7, bottom, were not significantly different.

All 15 patients rated themselves "improved" with the addition of pergolide compared with carbidopa-levodopa alone (seven-point global evaluation scale); 13 were self-rated as "moderately improved" or "markedly improved." The separate physician-scored global evaluations were essentially identical. Patients were also asked to compare MK-458 (HPMC) with pergolide. Eight patients believed that they achieved better control of their parkinsonism with pergolide, whereas six patients chose MK-458 (HPMC) (Table 5). Patients' rating scale comparisons of the side effects revealed no major trend favoring either medication (Table 5).

Table 5.—Patients' Self-evaluations of MK-458 (HPMC) and Pergolide Therapies

	Evaluation, No. of Patients						
	Better With MK-458 (HPMC)				Better With Pergolide		
	Very Much	Much	Slightly	No Difference	Slightly	Much	Very Much
Control of parkinsonism	1	3	2	1	5	2	1
Side effects	0	1	4	8	1	1	0

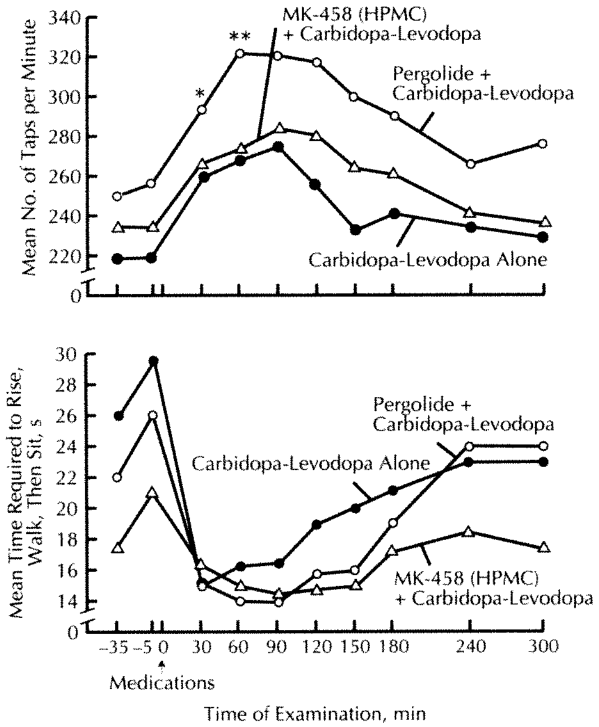

Fig 7.—*Comparison of finger-tapping speed (top) and results of the rise, walk, then sit test (bottom) in the 15 patients completing all three phases of the study (carbidopa-levodopa alone, adjunctive MK-458 [hydroxypropylmethylcellulose or HPMC], and adjunctive pergolide). Top, For tapping speed, pergolide vs MK-458 (hydroxypropylmethylcellulose/lactose [HPMC]): single asterisk indicates P<.05; double asterisk, P<.01. Bottom, There were no significant differences between the median pergolide and MK-458 (HPMC) data points on the timed walking measures.*

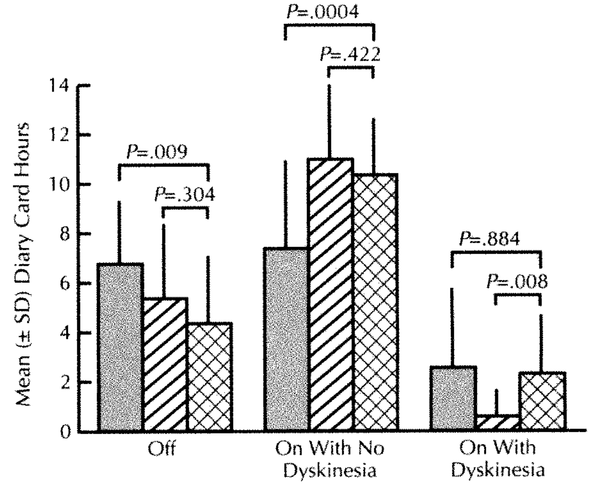

Fig 8.—*Comparison of mean diary card data in the three phases of this investigation. The time for "on with dyskinesia" was significantly less with MK-458 (hydroxypropylmethylcellulose/lactose [HPMC]) than with pergolide (P<.01). There were no statistically significant differences in "off" time or "on with no dyskinesia" between the pergolide and MK-458 (HPMC) phases. Shaded bars indicate carbidopa-levodopa alone; hatched bars, MK-458 (HPMC) plus carbidopa-levodopa; and cross-hatched bars, pergolide plus carbidopa-levodopa.*

The mean 4-day diary card data suggested a slight trend toward less off-time with pergolide than with MK-458 (HPMC), but this difference did not reach statistical significance (Fig 8). Although the "on-time with no dyskinesia" was similar with MK-458 (HPMC) and pergolide, the "on-time with dyskinesia" was significantly less with MK-458 (HPMC) than with pergolide (Fig 8; $P<.01$).

The mean score on the Northwestern University Disability Scale improved from 11.7 (baseline) to 10.0 with MK-458 (HPMC) ($P<.05$) and improved further to 6.8 during the pergolide trial ($P<.01$, compared with baseline). The lower score during the pergolide phase was not statistically different from the score during the MK-458 (HPMC) phase.

The adverse events during the pergolide phase, apart from those already described among the patients who dropped out, were largely restricted to nausea; six of the 15 patients reported this side effect. One patient each complained of the following side effects: hypomania, drowsiness, chest pain, rash, and change in hair texture. No patients experienced paradoxical freezing during the pergolide phase. Because side effects were monitored much less closely during the pergolide phase, comparison of adverse events with the MK-458 (HPMC) phase would not be valid.

COMMENT

MK-458 (HPMC) used as adjunctive therapy with carbidopa-levodopa resulted in significant improvement in the control of Parkinson's disease symptoms and signs but not to the degree we had expected based on in vivo data from studies involving laboratory animals.[8,9] These in vivo studies have found MK-458 to be a considerably more potent D-2 agonist than various other drugs, including pergolide and bromocriptine.[8-10] If the D-2 receptor is primarily responsible for mediating the antiparkinsonian response,[6,7] one might have expected this medication to elicit a much more dramatic effect. The absence of a more favorable response to MK-458 (HPMC) cannot be attributed to inadequate dosage. First, the dosage was increased well beyond that used in early studies of MK-458. Second, the antiparkinsonian response to this medication plateaued before the maximal allowed dose was reached (Fig 5). Prior studies have suggested adequate bioavailability of the controlled-release (HPMC) formulation of MK-458 (Gilbert A. Block, MD, PhD, oral communication, 1990). A recently published study[38] employing high doses of MK-458 (HPMC), similar to those used in our investigation, also found benefits that were less dramatic than expected.

This investigation also demonstrated a substantially greater antiparkinsonian response to pergolide than to MK-458 (HPMC). In addition, pergolide elicited more prominent dyskinesias than MK-458 (HPMC). We chose pergolide for comparison with MK-458 because of the distinct difference in pharmacologic properties. MK-458 is a very potent D-2 receptor agonist[8-10] but has no D-1 agonist properties.[8,9,11-15] In comparison, pergolide is a considerably less potent D-2 agonist, according to in vivo studies,[8-10] but has D-1 agonist activity.[19-22]

These results are consistent with those of various animal studies published during the past few years that indicate that D-1 receptor stimulation contributes to the motor response to dopamine.[23-29,32,33] These investigations have revealed that the interaction between D-1 and D-2 receptors is not simply additive but synergistic; this observation has been demonstrated not only in animal models of parkinsonian-related behavior[23,26-29,32] but also in neurophysiologic studies of single-unit activity in the neurons of the substantia nigra and globus pallidus.[30,31]

Our results suggest that D-1 stimulation facilitates not only antiparkinsonian responses but also choreiform side effects. The peak-dose dyskinesias experienced by the patients in all phases of this study were predominantly of the choreiform type. The selective D-2 agonist MK-458 elicited comparatively less dyskinesia than the combined D-1 and D-2 agonist pergolide, according to both the medication-response profile data and the diary card entries. Adjunctive therapy with MK-458 (HPMC) also elicited less dyskinesia than did therapy with carbidopa-levodopa alone. These findings are consistent with those of primate studies demonstrating that D-1 receptor stimulation appears to be critical to the elicitation of chorea.[7] This observation suggests that pure D-2 agonists may have a role in the treatment of patients whose primary complaint is medication-induced chorea. However, this possibility requires further study.

Clinical comparison of a selective D-2 agonist with a combined D-1 and D-2 agonist has been limited to only a few studies of patients with Parkinson's disease. Several investigators have noted that patients who exhibit deteriorating responses to the D-2 agonist bromocriptine improved after a transition to pergolide therapy.[39-41] Lees and Stern[42] found pergolide to be superior to the D-2 agonist lisuride in the treatment of patients with fluctuating responses to levodopa. Like MK-458, bromocriptine and lisuride are devoid of D-1 agonist activity[22]; hence, these results parallel our findings. However, LeWitt et al[43] found pergolide and bromocriptine to be clinically comparable when added to carbidopa-levodopa in a double-blind crossover study. Precise measurement of the peak medication responses and response durations were not performed by LeWitt et al, and less than dramatic differences could have gone undetected.

Paradoxical freezing was experienced by approximately one third of patients when administered the highest doses of MK-458 (HPMC). This effect occurred during the time of the peak medication response. It resolved with MK-458 dose reduction. In our experience, such paradoxical freezing is only very rarely associated with carbidopa-levodopa alone. We see it occasionally in patients taking higher doses of bromocriptine or pergolide in combination with carbidopa-levodopa but not nearly as frequently as observed in this study of MK-458 (HPMC). This finding is in contrast to the typical observation that gait hesitancy or freezing observed in patients receiving low doses of dopamine-active medications often improves with medication increments, although not all patients with freezing respond to dose escalation. Apparently, gait hesitancy or freezing can reflect various conditions: (1) a dopamine insufficiency state, (2) excessive D-2 stimulation, or (3) impairment of nondopamine neuronal networks.

In summary, the results of this study suggest that a combined D-1 and D-2 agonist is superior to a pure D-2 agonist in suppressing symptoms of Parkinson's disease in patients with fluctuating responses to levodopa. However, administration of a pure D-2 agonist (such as MK-458) may be less likely to induce dyskinesias than a combined D-1 and D-2 agonist. These results should be considered preliminary because of the uncontrolled study design. Nonetheless, the results are consistent with increasing evidence that D-1 receptor stimulation contributes to motor responses to dopamine.

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Brain Death

Occurs Only With Destruction of the Cerebral Hemispheres and the Brain Stem

James L. Bernat, MD

Brain death is the colloquial term used when human death is determined by tests showing global brain destruction or irreversible cessation of global brain functions. Since the original delineation of this concept in 1959, with few exceptions, Western society has evolved a consensus that brain death represents the medical, philosophical, and legal standard of human death. This societal consensus has permitted the statutory recognition of brain death in about 90% of the states in the United States and in many other Western countries.

All accepted medical tests to determine brain death and all enacted statutes of brain death utilize the "whole-brain" criterion of death: death is the irreversible cessation of hemispheric and brain-stem neuronal functions. Physicians have constructed batteries of bedside and confirmatory laboratory tests to show that this criterion of death has been satisfied. Tests to demonstrate absence of the brain-stem functions are pivotal to all published batteries of brain death tests. All require unresponsive coma, apnea, and the absence of brain-stem (pupillary, corneal, vestibulo-ocular, gag, and cough) reflexes.[1]

Previously, I provided a philosophical defense of the whole brain criterion of death by showing that it is the necessary and sufficient condition for the most plausible definition (concept) of death. I proposed that death is best defined as the permanent cessation of functioning of the organism as a whole. Such functions include respiration, circulation, consciousness, and homeostatic responses to internal and external stimuli that favor the continued health of the organism. This definition made explicit the implicit definition underlying our traditional concept of death without altering that concept.[2,3]

More recently, I clarified that the whole-brain criterion of death does not require the cessation of function of *every* neuron in the brain. Rather, it requires that a *critical* number of neurons permanently cease functioning, namely, those that subserve the essential activities of the hemispheres, diencephalon, and brain stem. It is these neuronal networks that execute the functions of the organism as a whole.

In most cases of brain death, all measurable intracranial neuronal functions cease. However, in some cases, a critical number of neurons have been destroyed but a few continue to function in isolation. For example, some unequivocally whole–brain-dead patients continue to manifest rudimentary but recordable electroencephalographic activity or hypothalamic neuroendocrine activity sufficient to prevent diabetes insipidus.[4] Because these isolated nests of independently operating neurons no longer contribute critically to the functions of the organism as a whole, their continued activity remains consistent with the whole-brain criterion of death.

During the past two decades, a group of philosophers and physicians have advocated replacing the whole-brain criterion of death with the "higher-brain" criterion of death. According to this theory, death represents "the irreversible loss of that which is significant to the nature of man." Higher-brain constructionists hold that irreversible loss of consciousness and cognition is necessary and sufficient for death. According to this formulation, the continued functioning of the brain stem is consistent with death; all that is required is cessation of functioning of the cerebral hemispheres.[5] Using this criterion, patients in persistent vegetative states, others with advanced forms of dementia, and anencephalic infants would be classified as dead.

Several flaws of the higher-brain formulation render it unsatisfactory as a concept of death: (1) by classifying patients as dead who are considered alive in every society, the higher-brain formulation is a radical redefinition of death; (2) it is arbitrary to stipulate the degree of brain damage necessary for death because states of bilateral hemispheric neuronal damage form a continuum from mild to profound; (3) there is no reliable test for the higher-brain criterion; assessing prognosis with a high degree of certainty requires weeks or months of observation for patients in vegetative states,[6] and it is counterintuitive to argue that physicians must observe patients for that duration to determine whether or not they are dead; and (4) practical problems arise concerning burial practices: should the "dead" patient be buried while still exhibiting breathing, heartbeat, and gag and cough reflexes? We are revulsed by this idea because at an intuitive level we recognize that such patients are alive.

The higher-brain formulation was devised to solve the problem of what to do with the patient in a persistent vegetative state. It is true that many people consider pa-

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tients in states of permanent unawareness "as good as dead" and that most people would not desire to continue living if they were in such a hopeless, meaningless state. However, now that acceptable medical practices exist permitting termination of treatment that allows such patients to die,[7,8] it is unnecessary to contrive that they are already dead. Unjustifiably redefining live patients as dead destroys the serviceable concept of whole-brain death that accurately portrays biological reality and has achieved a high level of acceptance by Western society.

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Defining Death

A Superficial and Fragile Consensus

Stuart J. Youngner, MD

Beauchamp and Childress, in their *Principles of Biomedical Ethics*, describe how an African tribe, the Nuer, used a conceptual ploy to circumvent a moral prohibition against killing unwanted newborns.[1]

> . . . the Nuer tribe viewed defective newborns as nonhuman "hippopotamuses" who were mistakenly born to human parents and who would be put in the river, which was viewed as their natural habitat.

Does our own society's rapid and widespread embrace of so-called brain death represent a similar form of conceptual gerrymandering? A review of the social, medical, and public policy developments of the last two decades leaves the answer to this question in doubt.

In 1968, an ad hoc committee at the Harvard Medical School, Boston, Mass, proposed "a new criterion for death": total and irreversible loss of functioning of the whole brain.[2] The motivation was clearly stated as follows: (1) to relieve the "burden" imposed by severely brain-damaged patients; and (2) to quell the "controversy in obtaining organs for transplantation."

Was the ad hoc committee, like the Nuer tribe, using a conceptual ploy to sidestep a moral dilemma? Was it simply easier to declare these patients dead than to let them die by discontinuing life support or to kill them by taking out their hearts and kidneys? Or had the advent of the ventilator and the intensive care unit simply caused a reexamination of the traditional ways of distinguishing between the life and death of a human being?

A formulation of death must have three components: a concept or *definition* of what it means to die, operational *criteria* for determining that death has occurred, and specific medical *tests* showing whether or not the criteria have been fulfilled.[3-5] While the ad hoc committee offered a criterion for determining death (irreversible loss of all brain function), it did not provide a conceptual framework for answering the question, "What quality is so essentially significant to a living entity that its loss constitutes the death of that entity?"

Despite the lack of a clear concept behind it, the whole-brain criterion gained rapid and widespread acceptance. In fact, it was not until 13 years had passed (1981) that James Bernat and his colleagues offered the first comprehensive effort to provide a conceptual framework for the ad hoc committee's criterion.[5] "We define death," they wrote, "as the permanent cessation of functioning of the organism as a whole," which they further explained as "the spontaneous and innate activities carried out by the integration of all or most subsystems." They claimed that this concept was valid because it reflected the meaning of death in everyday use and encompassed the traditional meaning of death.

Were they correct? Had the whole-brain criterion finally, after 13 years, found a conceptual validation? And was this validation, offered by Bernat and his colleagues, not only correct, but also the very one we had understood all along? I think not.

The whole-brain criterion for determining and declaring patients dead (ie, brain death) was accepted by our

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society for two very practical reasons that had little to do with whether or not "brain death" is equivalent to death: (1) irreversible loss of all brain function is easy to diagnose in adults—a well-trained neurologist, neurosurgeon, or critical care physician can do so at the bedside on the basis of clinical examination alone; and (2) once the diagnosis is clear, so also is the prognosis. In fact, no patient with irreversible loss of all brain function has either (1) regained consciousness or (2)"lived" for more than hours, days or, in a few instances, weeks—despite the most aggressive treatment possible. In fact, the diagnosis of and prognosis for these patients is as certain as anything in clinical medicine.

It is this bundle of characteristics plus the irresistible utilitarian appeal of organ transplantation that led to the apparent acceptance of brain death.

If we look closely, however, we can see that many persons are ambivalent or confused about the status of brain-dead patients. Moreover, many who believe brain-dead patients are dead do so because such patients have irreversibly lost the higher brain functions of consciousness and cognition, rather than the brain-stem's integrative capacity central to Bernat's concept of death.

If the credibility of a concept should be judged by the everyday use of language, it is interesting to observe how the term *brain death* stubbornly persists to describe those patients who are legally dead according to its criteria. Newspaper stories regularly describe how brain-dead patients are being "kept alive" in intensive care units, only to "die" when "life-support" systems are withdrawn. This type of paradoxical speech is also the rule among health professionals, who, in my experience, almost never refer to patients who have lost all brain function as "dead," but consistently and insistently call them "brain dead," noting the time of death on death certificates as the moment the heart stopped beating. If loss of integrating function is what everyone means by death, then why do we not simply use the word dead?

The persistent use of the term brain-dead distresses the transplantation community, who views it as an impediment to optimal organ retrieval. But the stubborn persistence of brain death in our everyday language is not simply a slip of the tongue or ignorance of the facts. It reflects an underlying confusion about the true state of patients whose brains have stopped functioning, but whose cells, tissues, organs, and organ systems continue to live—integrated, however modestly, by the machines and staff of our modern intensive care units.

In a study of 195 physicians and nurses likely to be involved in organ procurement for transplantation, my colleagues and I discovered considerable trouble in understanding the concept of brain death.[6] The sample included intensive care unit physicians and nurses, neurosurgeons, operating room nurses, and anesthesiologists. Among other things, we attempted to elicit respondents' underlying *concepts* of death, ie, which specific brain functions they considered to be so essential or fundamental that their absence is equated with the death of a patient. We presented each study subject with two cases, one a patient with irreversible loss of all brain function (brain dead) who was being maintained on life-support systems, and second, a patient in a persistent vegetative state (PVS).

While the vast majority (95%) said that in their personal opinion, leaving aside legalities, the brain-dead patient was dead, a sizeable minority (38%) also thought the PVS patient was dead. When we asked the 185 respondents who said they thought the brain-dead patient was dead to offer a concept that explained why the patient was dead, 25% said that "integrating capacity" or "the ability of the organism to function as a whole" was the essential function that had been lost. Interestingly, more persons (36%) gave a higher brain concept—the loss of consciousness and cognition—to explain why the brain-dead patient was dead. Most interesting, perhaps, was the fact that fully 32% of respondents gave answers indicating that although they stated that the brain-dead patient was dead, they did not really believe it. When asked what made a brain-dead patient dead, they answered either that no matter what was done the patient would die soon anyway or that the patient's quality of life was unacceptable.

The persistence of the term *brain death* in everyday language and the results of our study indicate that our society is still confused and divided about newer ways of defining death. The clinical characteristics of brain-dead patients and the pressing need for organs have allowed us to adopt certain practices as policy while a considerable degree of conceptual disarray continues.

Bernat and his colleagues offered one cogent philosophical explanation of why brain-dead patients are indeed dead. A competing explanation, based on the higher brain functions of consciousness and cognition, has been more widely endorsed in the philosophic[7,8] and, if our study was indicative, the medical community as well. Such reasoning has even been embraced by a Supreme Court judge. In the recent Cruzan decision, Justice Stevens wrote, "there is a serious question as to whether the mere persistence of their [PVS patients'] bodies is 'life' as that word is commonly understood, or as it is used in both the Constitution and the Declaration of Independence."[9] It is also clear that many other persons are not completely comfortable calling someone dead until the heartbeat and respirations irreversibly cease, and all vital functions cease. In fact, the state of New Jersey has adopted a policy that allows family members to veto a declaration of death because of religious belief, ie, their brain-dead relative must be declared dead by traditional criteria.

Such disagreement and confusion are not without consequences. Confusion about brain death may be one of the factors impeding effective communication with families about their option to donate organs. It has also led for calls to "define" anencephalic infants as dead, a blatant case of conceptual gerrymandering. As the shortage of organs for transplantation grows will we also hear calls to define PVS patients as dead so we can take their organs? Will public policy continue to press forward the agenda of medical science at a faster pace than our society can digest its deeper moral and cultural implications?

Before the advent of the modern intensive care unit, death occurred more or less at once. Now we have the ability to tease apart the various components of human life, keeping some going while others have been irretrievably lost. Thus, we are forced to choose among various functions and levels of organization of life, declaring death, sometimes, when life of some sort remains, a palpable and painful reminder of the loved one or patient that no longer lives. Our ability to draw clear lines will be complicated as we attempt to incorporate persons from diverse religious and cultural traditions into an already heterogeneous society. We have not heard the end of the debate about defining death.

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Brain Death or Loss of Human Brain Life?

Death, like birth, is a mystery of nature, it presupposes the arrangement and disarrangement of certain elements" according to Marcus Aurelius. Bernat thinks that for the brain the elements are "a critical number of neurons (that) permanently cease functioning, namely, those that subserve the activities of the hemispheres, diencephalon, and brain stem. It is these networks that execute the functions of the organism as a whole."

Youngner does not articulate an alternate definition but points out that many who believe that brain-dead patients are dead do so "because such patients have irreversibly lost the higher brain functions of consciousness and cognition." He also alludes to the findings of a study that he and his colleagues carried out in 195 physicians and nurses likely to be involved in organ procurement for transplantation in which 38% of respondents considered patients in a persistent vegetative state as brain dead. In such cases, the patient may still be able to withdraw a limb to pain but is not conscious of the act nor understands its meaning. Bernat's definition of brain death includes the permanent cessation of function of neurons "that subserve the essential activities of the hemispheres." It is reasonable to presume that these essential functions include awareness of self and the appreciation of meaning.

The term *brain death* implies irreversibility and finality that make easier the decision of relatives to grant permission for organ donation or discontinuation of life support systems. On the other hand, it contradicts the concept of death as total loss, as illustrated by Youngner and coworkers' 32% of respondents who stated that a patient was brain dead but did not really believe it.

Perhaps the crux of the issue is not brain death but *loss of human brain life*, implying awareness and understanding. The loss of these functions coupled with the loss of hope for their recovery may form the basis for discontinuing the support of vegetative survival.

—VLADIMIR HACHINSKI, MD, DSC(MED)

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Professional Opportunities

VERY BUSY SOLO practice neurologist in northeast Ohio looking for an aggressive partner. $100,000 first year, partnership in two years. No buy in. Send CV to: Box #824, c/o AON.

FLORIDA: If you are a BC/BE neurologist interested in associating with a solo neurologist in a beautiful east central coastal Florida city, please send your CV to: John LoZito, MD, 1400 Pine Street, Melbourne, FL 32901.

Professional Opportunities

HAVEN FOR outdoor enthusiasts – Beautiful Escanaba, Michigan is seeking a neurologist to establish a busy practice in a 50,000 population service area, currently without a neurologist. A confident generalist will be immediately productive with established patient base and practice support from Saint Francis Hospital. Resort community offers unspoiled natural beauty, Hiawatha National Forest, Little Bays de Noc and harbor, abundant summer and winter sports, boating, legendary fishing, hiking, skiing and snowmobiling. Healthy lifestyle; good schools; friendly community. Contact: Dawn Hamman, Saint Francis, Inc., 4541 North Prospect, Suite 400, Peoria, IL 61614. (800) 232-3129.

INDIANAPOLIS METROPOLITAN AREA: Young and aggressive Indianapolis neurological group seeks board-eligible or -certified associate. Broad spectrum of clinical experience is important. Experience in EEG, evoked potentials and EMG is necessary. Sub-specialty training is desirable, but not necessary. Indianapolis is a desirable, growing, clean and safe community. Excellent salary plus bonus and benefits leading to stock holder opportunity. Send CV to: Midwest Neurological Institute, 998 East Main Street, #202, Danville, IN 46122.

NEUROLOGIST WITH EEG, EMG and evoked potential experience for busy neurology office. Full-time position. Heavy Spanish, oriental (Japanese, Chinese, Vietnamese and Korean) population. Los Angeles area. (213) 733-4891.

STROKE NEUROLOGIST: Well known, well established neurosurgical and neurological group practice in western Massachusetts seeks BC/BE neurologist with special training in stroke to join busy practice and to help establish a stroke unit at the Baystate Medical Center, a 900-bed teaching hospital and the western campus of Tufts Medical School. Clinical research available. Send CV to: Michael R. Sorrell, MD, 80 Congress Street, Springfield, MA 01104.

CHARLOTTE, NORTH CAROLINA: High quality group of five neurologists all of whom are subspecialized, seeks to add another well-trained neurologist. Contact: Fred Pfeiffer, MD, 1900 Randolph Road, Suite 1010, Charlotte, NC 28207. Or call: (704) 334-7311.

NORTHERN VIRGINIA
SUBURBS OF WASHINGTON, DC

Neurologist wanted with good interpersonal and practice development skills (subspecialty training desirable) to join multi-office neuroscience group. Position available immediately. Send CV to:
Jon Peters, MD
1800 Town Center Drive, #419, Reston, VA 22090

NEUROSURGEON – BC or BE to join another neurosurgeon at prestigious multi-specialty group in upper midwest capitol city. Sportsman's paradise. Clinic adjoins 260-bed tertiary care center with NS designated OR. Reply to: Box #839, c/o AON.

KANSAS – Board-certified, board-eligible neurologist to join child neurologist in rebuilding a three-person practice in the largest city in Kansas. Three large, well-equipped hospitals available for resident and undergraduate medical education. Located in clean, progressive community described as the franchise capital of the country. Competitive salary and benefits available. Send CV to: Richard C. Gilmartin, MD, 2620 East Central, Wichita, KS 67214.

Professional Opportunities

SOUTHEAST – Two neurologists, BC/BE to establish practice on hospital campus. Generous income guaranteed for two years. Large referral base, catchment area population of 350,000. All neuro-diagnostic modalities needed. Proficiency in EMG, EEG, CT, and MRI preferred. Inpatient and outpatient experience necessary. Metropolitan community offers many cultural, academic and recreational activities. Yes, it's still possible to have it all: a thriving practice in supportive medical community, affordable lifestyle, mild climate, and Atlanta is two hours away. Immediate openings. For more information, call: Nancy Stallings, CompHealth, (800) 328-3044; 4021 South 700 East, Suite 300, Salt Lake City, UT 84107.

NEUROLOGIST, BC/BE with strong clinical skills to join two neurologists and part-time neuropsychologist in southeastern Wisconsin. Located thirty minutes south of Milwaukee and sixty minutes north of Chicago on Lake Michigan. Rapidly expanding practice. Salary competitive and commensurate with experience. Contact: Raymond J. Rybicki, MD, (414) 631-8550. Or send CV to: 3803 Spring Street, Suite 201, Racine, WI 53405.

NEUROLOGIST

Beautiful Durango, Colorado is recruiting a BC/BE neurologist. Mercy Medical Center is an extremely progressive and active 100-bed facility and is doing well financially and growing, primarily due to an excellent staff of 94 physicians and a decent economy. Durango is located in southwestern Colorado, with an abundance of outdoor recreation (skiing, bicycling, fishing, hunting), wonderful restaurants, an excellent 4-year state college, great weather and outstanding schools! For more information about this excellent practice opportunity, mail CV or call: Bob Conrad, Vice President, Mercy Medical Center, 375 East Park Avenue, Durango, CO 81301. (303) 247-4311; or Dr. Benjamin Crue, (303) 259-0779.

NEUROLOGIST – Adult neurologist to join a 21-physician internal medicine group practice, currently including two neurologists. Subspecialty training will be strongly considered. Emergency call rotation currently includes six neurologists. Full neurodiagnostic capabilities available both in the office and at the teaching hospital. Growing area of coastal North Carolina, 250,000 referral area. Excellent industrial base, 7,500-student university campus, year round sailing, golfing, tennis, fishing, and other recreational opportunities. 500-bed tertiary care hospital, internal medicine residency program, academic affiliation with UNC-Chapel Hill. Full benefit package, competitive salary, EOE. CV to: Patrick Medeiros, Wilmington Health Associates, 1202 Medical Center Drive, Wilmington, NC 28401.

MANHATTAN – Faculty and private practice opportunities currently available at university-affiliated hospital with two new hospital facilities scheduled for completion 1992-1994. Neurologists with fellowship training in stroke, movement disorders and intensive care neurology are sought. Applicants should send CV to: Dr. Carl Braun, Chief, Division of Neurology, St. Luke's-Roosevelt Hospital Center, 1090 Amsterdam Avenue, New York, NY 10025.

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Highly competitive salary and fringe benefits with early partnership.

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Professional Opportunities

NEUROLOGIST – BC or BE, to join another neurologist at prestigious multi-specialty group in upper midwest capitol city. Sportsman's paradise. Clinic adjoins 260-bed tertiary care hospital. Reply to Box #839, c/o AON.

BC/BE NEUROLOGIST with subspecialty interests for multi-subspecialty neurology center in Tulsa. Adjacent to progressive 895-bed hospital with MRI, CT, EMG, EEG and Transcranial Doppler. Tulsa, a city of 500,000, is nationally recognized for its beauty, quality of life and recreational opportunities. Competitive salary and benefits package leading to early partnership. Send CV to: Stan Schuermann, 2003 Creighton Drive, Norman, OK 73071. Or call: (800) 332-8663, day or evening.

NORTHEAST TENNESSEE

Seeking BE/BC neurologist to join four physician group. Very competitive salary, excellent benefits, bonus incentives, shared call coverage, paid site visit and relocation expenses. Tri-Cities ranked 7th Best Place to Live in U.S.. MSA 400,000+. 422-bed teaching facility currently constructing region's new premier hospital to be completed by Winter '93. Ancillary services include: Sleep Disorder Laboratory, Neuroscience Center, 2 CT's, 2 MRI's, 60,000 patients/year in 24 hour Level II Trauma ER.

Send CV to: Cindy Hewa, Physician Recruiter,
Bristol Regional Medical Center
209 Memorial Drive, Bristol, TN 37620
Or call (800) 735-5433 • (615) 968-6775

NEUROLOGIST – BC/BE, with Spanish speaking skills, to join busy neurosurgical practice in San Antonio, Texas. Excellent salary and benefit package. Send CV: Box #842, c/o AON.

FULL-TIME NEUROLOGIST with research interest and experience in disorders of cognition and memory. Applicant must be neurology board-certified/-eligible and have completed a fellowship in areas related to cognition and memory. A multi-department cooperative unit is in place to provide an enriched clinical and research environment for this position. Interested applicants should send their curriculum vitae to: Frederick J. Samaha, MD, Department of Neurology, University of Cincinnati Medical Center, M.L. 525, Cincinnati, OH 45267. The University of Cincinnati is an EEO/AA employer. The review of applications will begin in March 1992 and continue until the position is filled.

ESTABLISHED NEUROLOGICAL GROUP practice located in picturesque Florida border town of Thomasville, Georgia, with a population of 35,000. Only minutes from Tallahassee, home of Florida State University and Florida's capital. Big city conveniences with small town charm. Fine area schools both public and private. Affordable housing and an abundance of recreational amenities include golf and hunting. Outstanding financial package. Paid interviewing and relocation expenses. Send CV or call: Steve Bible, Jackson and Coker, 115 Perimeter Center Place, Suite 380 11693, Atlanta, GA 30346. Telephone: (800) 544-1987.

MAUI ORTHOPEDIC and Sports Medicine seeks neurologist to establish independent practice. Contact: William Gfeller, 450 Hookahi Street, Wailuku, Maui, HI 96793. (808) 244-5541.

PROGRESSIVE AND PREEMINENT neurology group seeks fourth member in a quality-oriented practice. Davenport, Iowa, with a population of 300,000, boasts safe streets, nationally rated public schools and cultural amenities such as symphony and theatre. Salary of $130,000 and full benefits offered with a one year partnership option. This opportunity combines superb quality of life with a quality practice. Send CV or call: Joe Kelly, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 11683, Atlanta, GA 30346. Telephone: (800) 544-1987.

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Fellowships

NEUROLOGIST – The Michigan Head Pain and Neurological Institute (MHNI) seeks a BC/BE neurologist with strong clinical and communicative skills and special interest in head pain disorders. MHNI is a nationally recognized, fully accredited private center with a staff of 50, including three neurologists, an internist, PhD psychologists, and a neuropsychologist. Dedicated, 16-bed inpatient unit also available at nearby hospital. Enjoy an exceptional quality of life, very limited call, and all the amenities of Ann Arbor, Michigan. Outstanding financial package. Send CV or call: Todd Dillon, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 11655, Atlanta, GA 30346. Telephone: (800) 544-1987.

NEUROLOGIST with interest in art forms for research project in neuro-cellular and transmitter variations relative to visual and audial stimuli. Compensation open. Contact: Aesthetic & Neuronal Research Institute, 144 Grove Avenue, Cedarhurst, NY 11516. Attention: S.D. Bryman.

VIRGINIA – We are seeking a personable, clinically-oriented, BC/BE neurologist to join a group of four neurologists located in the Shenandoah Valley. Clinical experience in EMG, EEG, Doppler, CT and MRI desirable. 400-bed hospital with full neurodiagnostic laboratory and CT/MRI imaging center. Send cover letter describing yourself and copy of your CV to: Winchester Neurological Consultants, 125-A Medical Circle, Winchester, VA 22601. Attention: G. Steele.

Positions Available

ADULT NEUROLOGIST – Three-person, successful neurology group in beautiful Pennsylvania suburban community seeks additional member for clinical practice with academic affiliation. Teaching and research opportunities exist, subspecialty interest and/or fellowship desirable. Reply to: Box #840, c/o AON.

Directors Wanted

LOYOLA UNIVERSITY CHICAGO Stritch School of Medicine seeks Director of Stroke Program. Resources include transcranial Doppler, modern neuro-imaging laboratory with SPECT, and molecular neuroscience laboratories. Loyola University is a large center for cardiovascular disorders with very active surgical and cardiology programs. Research collaborations possible with cardiology and cardiovascular surgery. Candidates should be board-eligible or -certified neurologists with scholarly career interests and qualified for academic appointment. Send reply to: Gaston Celesia, MD, Chairman, Neurology Department, Loyola University, Chicago, 2160 South First Avenue, Chicago, IL 60153. Loyola is an equal opportunity/affirmative action employer.

THE DEPARTMENT OF NEUROLOGY at Creighton University has openings for BC/BE candidates as Director of the EMG Laboratory and Director of the Stroke Unit. Academic appointment, salary and support based on experience and academic record. Submit CV and three references to: John M. Bertoni, MD, PhD, Professor and Chairman of Neurology, Creighton University, 601 North 30th Street, Suite 2342, Omaha, NE 68131. (402) 280-4686. Creighton is an equal opportunity/affirmative action employer.

Residencies

NEUROLOGY – Unexpected opening PGYIII-IV to begin July, 1992. Contact: Dr. James Kelly, Box B182, University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver, CO 80262. (303) 270-8760. AA/EOE.

NEUROLOGY RESIDENCY PROGRAM–Dartmouth-Hitchcock Medical Center. PGYIII position available starting July 1, 1992. For information write: Alexander G. Reeves, MD, Professor and Chairman, Section of Neurology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756.

Faculty Positions

EPILEPTOLOGIST: The Department of Neurology at the University of Illinois at Chicago is recruiting an epileptologist at the level of assistant professor. The epileptologist will participate in drug trials for epilepsy, evaluation of epilepsy patients for neurosurgery, out-patient and in-patient management of epilepsy patients, and serve as co-director of an in-patient neuro-psychiatry unit. Candidate must have completed an accredited neurology residency and a fellowship in EEG or epilepsy, and must have special expertise in epilepsy. Contact: Daniel B. Hier, MD, Professor and Head, Department of Neurology, MC 796, University of Illinois at Chicago, Box 6998, Chicago, IL 60608. Or telephone: (312) 996-1757. UIC is an AA/EOE.

Neurologist wanted to join the Department at the El Paso Academic Campus of Texas Tech University Health Sciences Center. Medical students and resident rotations; opportunities for research. Reply with curriculum vitae to: Joseph B. Green, MD, Chairman, Department of Neurology, TTUHSC, Lubbock, TX 79430; or Albert Cuetter, MD, Associate Chairman, TTUHSC, 4800 Alberta Avenue, El Paso, TX 79905.

BE/BC NEUROLOGIST to participate in teaching, patient care and clinical research program. Subspecialty expertise desirable. Assistant professor, non-tenure earning position. Salary and benefits negotiable. May-September 1992 start. Contact: Leon D. Prockop, MD, Chairman, Neurology Department, (813) 974-2794. University of South Florida is an affirmative action/equal opportunity employer.

ACADEMIC POSITION AVAILABLE. Rank and salary dependent upon credentials. Interested applicants send curriculum vitae to: Dennis Lucy, MD, Department of Neurology, University of Arkansas College of Medicine, 4301 West Markham, Little Rock, AR 72205. An affirmative action/equal opportunity employer.

THE DEPARTMENT OF NEUROLOGY of the University of Iowa College of Medicine is actively recruiting new faculty. A research background is essential. Appointees are expected to conduct an active program of neuroscientific investigation. Areas of special emphasis are epilepsy, neuroimmunology and cerebrovascular diseases. Responsibilities include neurologic patient care and teaching of medical students and residents. All faculty serve in full-time status. Contact: Antonio R. Damasio, MD, Professor and Head, Department of Neurology, The University of Iowa, Iowa City, IA 52242. The University of Iowa is an affirmative action, equal opportunity employer. Women and minorities are encouraged to apply.

THE DEPARTMENT OF NEUROLOGY at the University of Massachusetts Medical Center is seeking a neurointensivist for a full-time position at the assistant or associate professor level, available by or before July 1992. A background and experience in electroencephalography and neurologic monitoring are desirable The proportion of time devoted to teaching, research and inpatient care is negotiable. Financial arrangements are competitive with similar institutions. Reply to: David A. Drachman, MD, Professor and Chairman, Department of Neurology, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655.

Fellowships

THE UCLA DIVISION of Neurosurgery is offering a visiting fellowship program in transcranial Doppler and cerebral blood flow monitoring. The three-day program provides comprehensive instruction in the clinical applications of transcranial Doppler and Xenon-133 cerebral blood flow monitoring. Instruction is provided with formal lectures and hands-on workshops. Course syllabus, workbook and certificate of completion are provided. Fee for the three-day course is $495 for physicians, and $395 for technologists. Dates: May 20-22; September 9-11; November 11-13. For further information and registration, please contact: UCLA Cerebral Blood Flow Laboratory, Division of Neurosurgery, CHS 74-140, 10833 Le Conte Avenue, Los Angeles, CA 90024-6901. (310) 206-0626; FAX (310) 825-7245.

Fellowships

BASIC NEUROSCIENCE FELLOWSHIPS for the Clinical Neuroscientist: A three-year NIH supported research fellowship is available immediately at the University of Minnesota. This is an exceptional opportunity for physicians who have completed their residencies in one of the clinical neurosciences (neurology, neurosurgery or neuropathology), who wish an academic career and who would like to obtain research experience in an area of basic neuroscience. There is a strong neuroscience community at the University of Minnesota and all participating faculty are part of the Graduate Program in Neuroscience. A wide variety of research opportunities are available including research in neuroanatomy, neurochemistry, neuroimmunology, neuropharmacology, neurophysiology, molecular neurobiology, and experimental neuropathology. Competitive stipends are provided. For further information, please contact: Gary Birnbaum, MD, Box 92, Mayo Building, University of Minnesota School of Medicine, Minneapolis, MN 55455. The University of Minnesota is an equal opportunity educator and employer.

CLINICAL NEUROPHYSIOLOGY/Epilepsy/Sleep Disorders Combined Fellowship – Offered for 1-2 years beginning July 1, 1992 at New England Medical Center and Tufts University School of Medicine, Boston, Massachusetts. The program offers training in pediatric/adult clinical EEG (including established computer techniques), drug studies in epilepsy and sleep disorders, video-EEG telemetry monitoring, presurgical cortical stimulation, intraoperative electrocorticography, polysomnography, and sleep disorders medicine (including neurology, psychiatry, ENT and pulmonary medicine). Candidates must be board-eligible in neurology and meet requirements for Massachusetts licensure. Applicants should send their CV and three references to: Bruce L. Ehrenberg, MD, New England Medical Center, EEG Department, 750 Washington Street, Boston, MA 02111; or call (617) 956-7504. New England Medical Center and Tufts University are affirmative action/equal opportunity employers.

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PRACTICE FOR SALE in beautiful northern California close to Stanford and Berkley. Unlimited potential for growth. Reply to: 4318C Valley Avenue, Pleasanton, CA 94566. Or call: (510) 462-2214.

Medical Meetings

ANNOUNCEMENT

Second International Conference
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in Lund, Sweden.

Registration and fee received by May 25, 1992
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For more information, contact:

Mrs. H.B. Franzen, Secretary
Department of Psychiatry
University Hospital
S-221 85 Lund, Sweden
Phone: 46-46-173887 • Fax: 46-46-110923

Miscellaneous

– CALL FOR PAPERS –

The International Conference
on Physician Health
to be held
January 28-31, 1993
in Scottsdale, Arizona

is accepting abstracts addressing topics related to physician health including AIDS, the HIV positive physician, problems related to aging, health promotion among physicians, mental illness, physical disability, and substance abuse among physicians. Possible topics for presentation include: Incidence of health problems, treatment issues, and legal implications of these disorders.

Abstracts which address issues related to these topics, but not dealing specifically with physicians are also welcome.

Submission Deadline: June 15, 1992.

Contact:

Patrick McGuffin, PhD
American Medical Association
Department of Mental Health
515 North State Street, Chicago, IL 60610
(312) 464-4064

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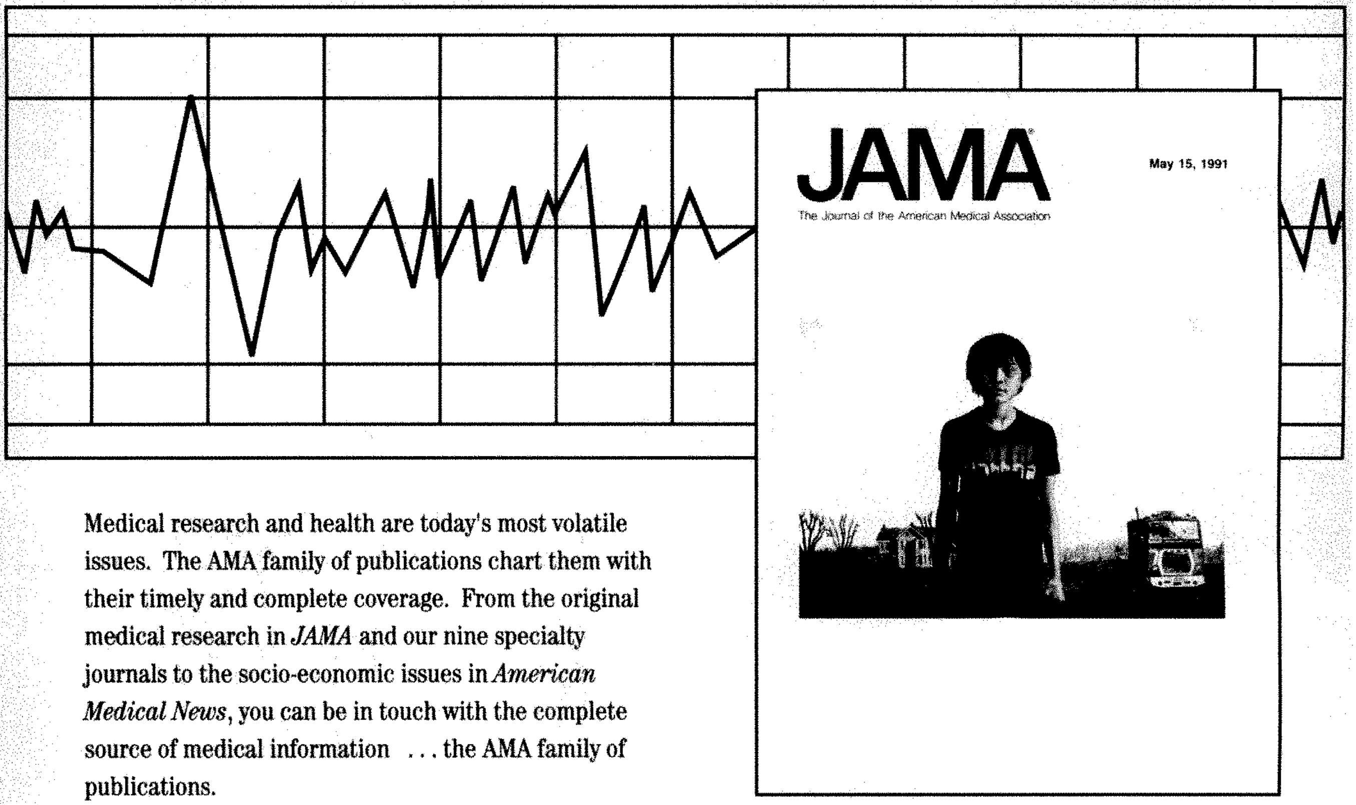
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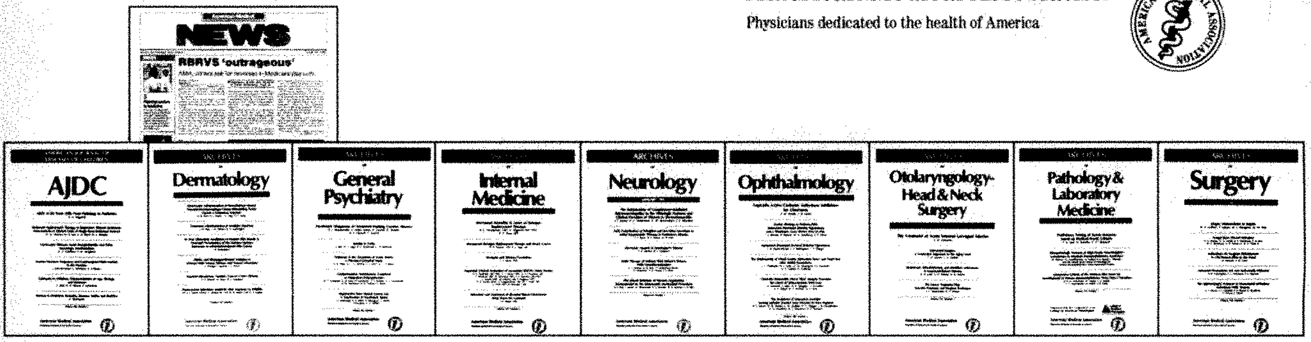

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INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See "Warnings" section for information on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, and immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Caution– Federal law prohibits dispensing without prescription. 0362G280

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References 1. Data on file, Market Research Dept, Parke-Davis. 2. Ramsay RE, Wilder BJ, Berger JR, Bruni J. A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology.* 1983;33:904-910. 3. Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin T. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *J Neurol Neurosurg Psychiatry.* 1985;48:639-644. 4. Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med.* 1985;313:145-151.

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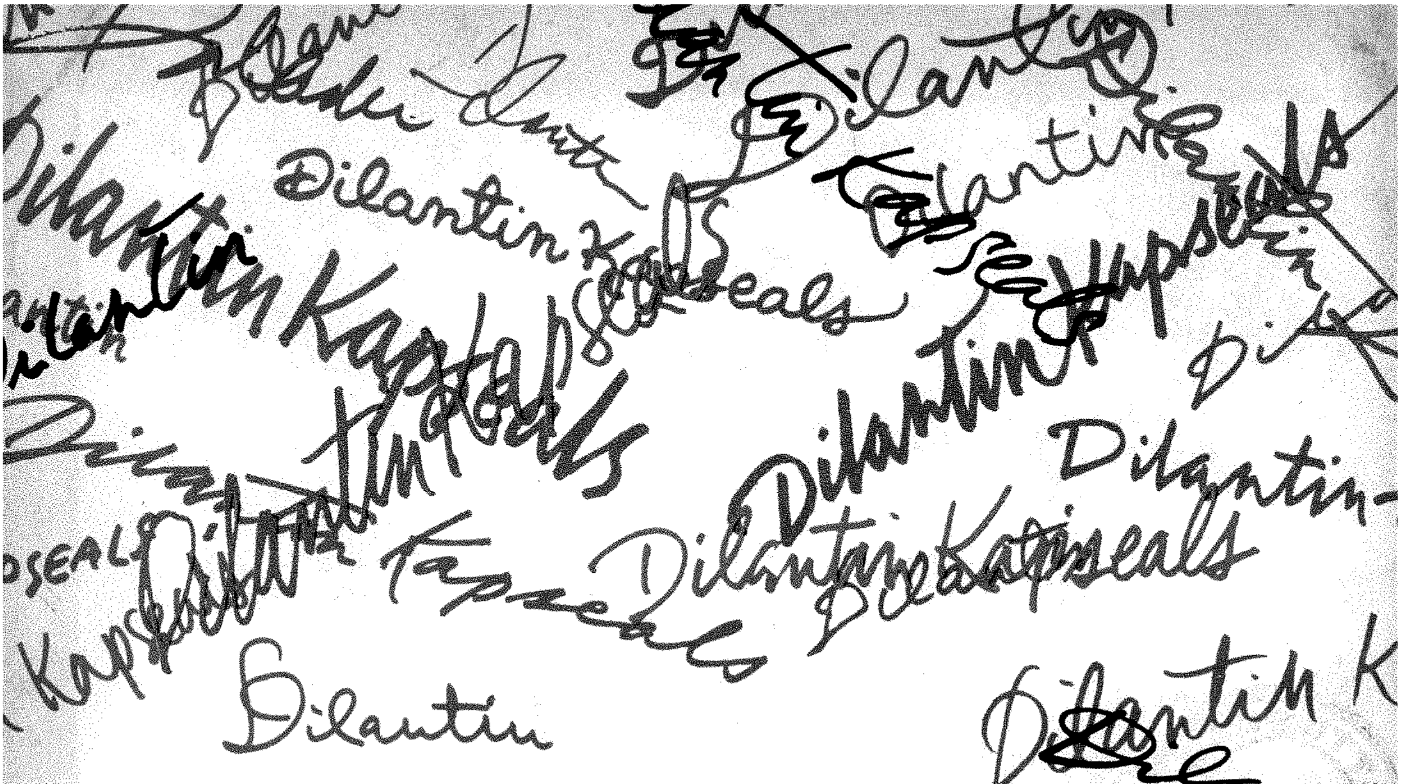

Thousands of neurologists go by the same name.

Neurologists write "Dilantin" more often than any other name in anticonvulsant therapy[1]—and for good reasons:

- **Unsurpassed control of generalized and partial seizures**[2-4]
- **Convenient once-daily dosing for many patients***
- **Significantly lower cost than carbamazepine or valproic acid**†

When you add billions of successful patient therapy days, it's clear why so many neurologists independently write the same prescription: Dilantin Kapseals for effective seizure control.

*For adult patients already controlled on 100 mg tid of Dilantin Kapseals.
†Adapted from *IMS National Pharmacy Audit Basic Data Book*, 4/91-6/91.[1]
Please see next page for a brief summary of full prescribing information.

Dilantin® Kapseals®
(extended phenytoin sodium capsules, USP) 100 mg
For control, compliance, and cost

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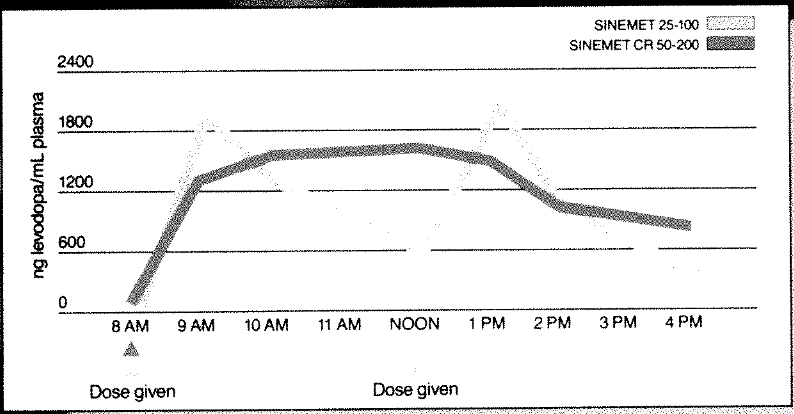
Volume 49, Number 6

American Medical Association
Physicians dedicated to the health of America

For many patients with Parkinson's disease

More Quality Time*

The causes of motor fluctuations are not completely understood; *in some patients* they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.



Smoother plasma levodopa levels[†1]

Less fluctuation of plasma levodopa levels with SINEMET CR vs SINEMET® (Carbidopa-Levodopa)

In a clinical trial, 14 patients with mild to moderate Parkinson's disease had plasma levodopa levels measured over 8 hours after one dose of SINEMET CR, and were compared with levels over the same period after two doses of SINEMET 25-100.

SINEMET® CR

(CARBIDOPA-LEVODOPA)
SUSTAINED-RELEASE

Before prescribing SINEMET CR, please see a Brief Summary of Full Prescribing Information on the third page of this advertisement.

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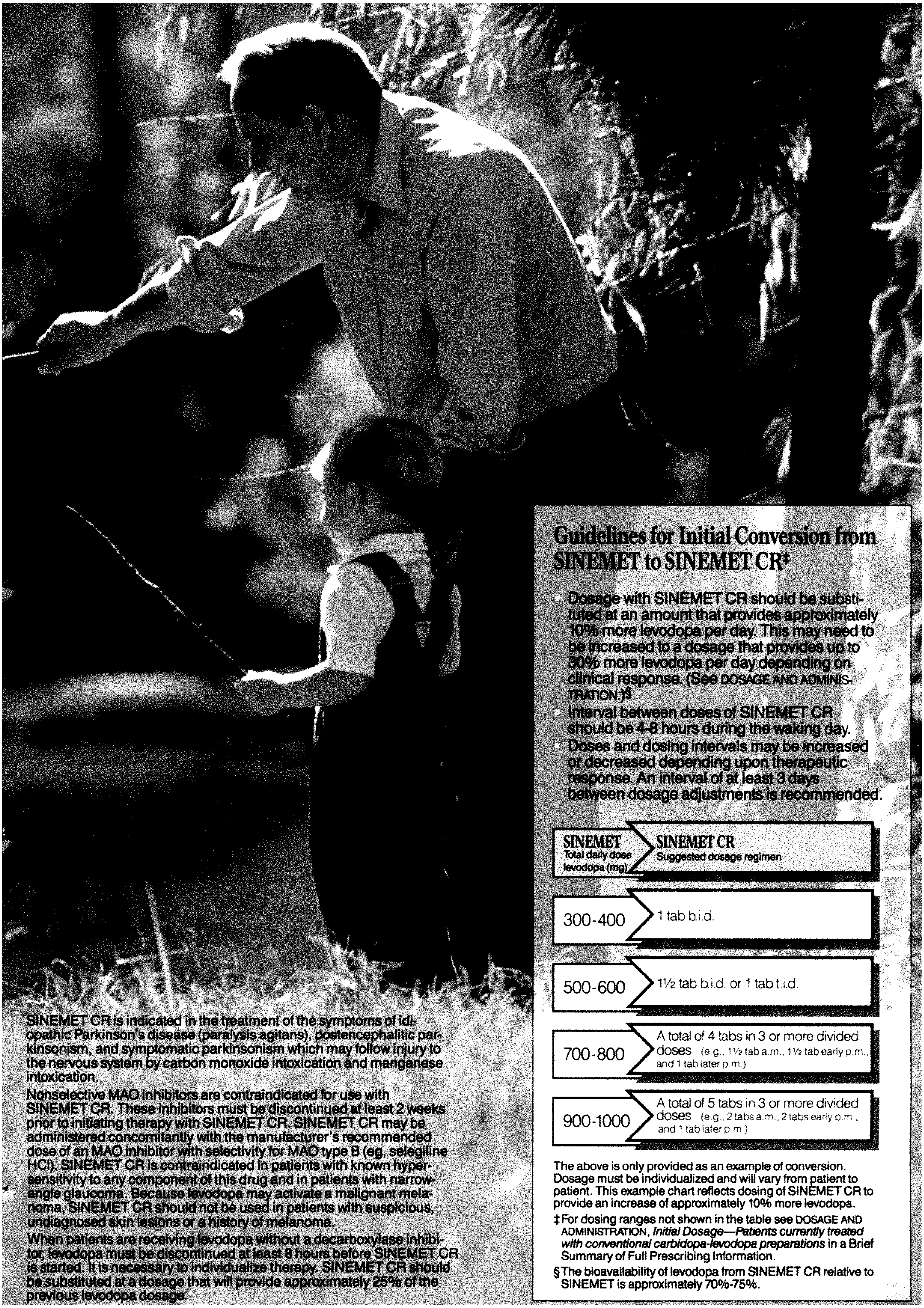
[*] Although in clinical trials, patients with moderate to severe motor fluctuations who received SINEMET® CR (Carbidopa-Levodopa) Sustained-Release *did not experience quantitatively significant reductions* in "off" time when compared to SINEMET, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET.

[†] Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET. The physician should be notified if such delayed responses pose a problem in treatment.

1. Goetz CG, Tanner CM, Shannon KM, et al. Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuations. *Neurology.* 1988;38:1143-1146.



Guidelines for Initial Conversion from SINEMET to SINEMET CR‡

- Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day. This may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response. (See DOSAGE AND ADMINISTRATION.)§
- Interval between doses of SINEMET CR should be 4-8 hours during the waking day.
- Doses and dosing intervals may be increased or decreased depending upon therapeutic response. An interval of at least 3 days between dosage adjustments is recommended.

SINEMET Total daily dose levodopa (mg)	**SINEMET CR** Suggested dosage regimen
300-400	1 tab b.i.d.
500-600	1½ tab b.i.d. or 1 tab t.i.d.
700-800	A total of 4 tabs in 3 or more divided doses (e.g., 1½ tab a.m., 1½ tab early p.m., and 1 tab later p.m.)
900-1000	A total of 5 tabs in 3 or more divided doses (e.g., 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

The above is only provided as an example of conversion. Dosage must be individualized and will vary from patient to patient. This example chart reflects dosing of SINEMET CR to provide an increase of approximately 10% more levodopa.

‡For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage—Patients currently treated with conventional carbidopa-levodopa preparations* in a Brief Summary of Full Prescribing Information.

§The bioavailability of levodopa from SINEMET CR relative to SINEMET is approximately 70%-75%.

SINEMET CR is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication.

Nonselective MAO inhibitors are contraindicated for use with SINEMET CR. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (eg, selegiline HCl). SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma. Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least 8 hours before SINEMET CR is started. It is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage.

SINEMET® CR (CARBIDOPA-LEVODOPA)

SUSTAINED-RELEASE TABLETS

CONTRAINDICATIONS Nonselective MAO inhibitors are contraindicated for use with SINEMET* CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl).

SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least eight hours before SINEMET CR is started. In order to reduce adverse reactions, it is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION).

Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, will occur at lower dosages and sooner during therapy with SINEMET CR (Carbidopa-Levodopa, Sustained-Release) than with levodopa alone.

As with levodopa, SINEMET CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution. The occurrence of dyskinesias may require dosage reduction.

Patients receiving SINEMET CR may develop increased dyskinesia compared to SINEMET (Carbidopa-Levodopa).

SINEMET CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET CR to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET CR may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

PRECAUTIONS **General** As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET CR provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Information for Patients The patient should be informed that SINEMET CR is a sustained-release formulation of carbidopa-levodopa which releases these ingredients over a 4 to 6 hour period. It is important that SINEMET CR be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

If abnormal involuntary movements appear or get worse during treatment with SINEMET CR, the physician should be notified, as dosage adjustment may be necessary.

Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET (Carbidopa-Levodopa). The physician should be notified if such delayed responses pose a problem in treatment.

Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.

NOTE: The suggested advice to patients being treated with SINEMET CR is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Laboratory Tests Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa-levodopa preparations than with levodopa.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions *Caution should be exercised when the following drugs are administered concomitantly with SINEMET CR (Carbidopa-Levodopa, Sustained-Release).*

Symptomatic postural hypotension has occurred when carbidopa-levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with SINEMET CR is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET CR should be carefully observed for loss of therapeutic response.

Carcinogenesis, Mutagenesis, Impairment of Fertility In a two-year bioassay of SINEMET (Carbidopa-Levodopa), no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

In reproduction studies with SINEMET (Carbidopa-Levodopa), no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

Pregnancy Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET (Carbidopa-Levodopa). There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. SINEMET (Carbidopa-Levodopa) caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. Use of SINEMET CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINEMET CR is administered to a nursing mother.

Pediatric Use Safety and effectiveness in infants and children have not been established, and use of the drug in patients below the age of 18 is not recommended.

ADVERSE REACTIONS In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations while on SINEMET (Carbidopa-Levodopa) were randomized to therapy with either SINEMET (Carbidopa-Levodopa) or SINEMET CR. The adverse experience frequency profile of SINEMET CR did not differ substantially from that of SINEMET (Carbidopa-Levodopa), as shown in Table 1.

Table 1 Clinical Adverse Experiences Occurring in 1% or Greater of Patients

Adverse Experience	**SINEMET CR** n=491 %	**SINEMET** (Carbidopa-Levodopa) n=524 %
Dyskinesia	16.5	12.2
Nausea	5.5	5.7
Hallucinations	3.9	3.2
Confusion	3.7	2.3
Dizziness	2.9	2.3
Depression	2.2	1.3
Urinary Tract Infection	2.2	2.3
Headache	2.0	1.9
Dream Abnormalities	1.8	0.8
Dystonia	1.8	0.8
Vomiting	1.8	1.9
Upper Respiratory Infection	1.8	1.0
Dyspnea	1.6	0.4
'On-Off' Phenomena	1.6	1.1
Back Pain	1.6	0.6
Dry Mouth	1.4	1.1
Anorexia	1.2	1.1
Diarrhea	1.2	0.6
Insomnia	1.2	1.0
Orthostatic Hypotension	1.0	1.1
Shoulder Pain	1.0	0.6
Chest Pain	1.0	0.8
Muscle Cramps	0.8	1.0
Paresthesia	0.8	1.1
Urinary Frequency	0.8	1.1
Dyspepsia	0.6	1.1
Constipation	0.2	1.5

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received SINEMET CR and 475 who received SINEMET (Carbidopa-Levodopa) during controlled clinical trials included: decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.

The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with SINEMET CR, listed by body system in order of decreasing frequency, include:

Nervous System/Psychiatric: Chorea, somnolence, falling, anxiety disorder, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.

Body as a Whole: Asthenia, fatigue, abdominal pain, orthostatic effects.

Digestive: Gastrointestinal pain, dysphagia, heartburn.

Cardiovascular: Palpitation, essential hypertension, hypotension, myocardial infarction.

Special Senses: Blurred vision.

Metabolic: Weight loss.

Skin: Rash.

Respiratory: Cough, pharyngeal pain, common cold.

Urogenital: Urinary incontinence.

Musculoskeletal: Leg pain.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

Other adverse experiences have been reported with various carbidopa-levodopa formulations and may occur with SINEMET CR:

Nervous System/Psychiatric: Mental changes including paranoid ideation, psychotic episodes, depression with suicidal tendencies and dementia; convulsions (however, a causal relationship has not been established); bradykinetic episodes.

Gastrointestinal: Gastrointestinal bleeding, development of duodenal ulcer.

Cardiovascular: Cardiac irregularities, phlebitis.

Hematologic: Hemolytic and nonhemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.

Laboratory Tests: Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, protein - bound iodine, Coombs test.

Other adverse reactions that have been reported with levodopa are:

Nervous System: Numbness, increased hand tremor, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome.

Psychiatric: Delusions, euphoria.

Gastrointestinal: Bitter taste, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.

Metabolic: Weight gain, edema.

Integumentary: Malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, loss of hair.

Genitourinary: Urinary retention, urinary incontinence, dark urine, priapism.

Miscellaneous: Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE Management of acute overdosage with SINEMET CR is the same as with levodopa. Pyridoxine is not effective in reversing the actions of SINEMET CR.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET CR should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION SINEMET CR tablets contain carbidopa (50 mg) and levodopa (200 mg) in a 1:4 ratio. The daily dosage of SINEMET CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of involuntary movements, dyskinesias or nausea. SINEMET CR may be administered as whole or as half-tablets which should not be chewed or crushed.

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while SINEMET CR is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Initial Dosage *Patients currently treated with conventional carbidopa-levodopa preparations:* Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see DOSAGE AND ADMINISTRATION, TITRATION). The interval between doses of SINEMET CR should be 4-8 hours during the waking day. *Patients currently treated with levodopa without a decarboxylase inhibitor:* Levodopa must be discontinued at least eight hours before therapy with SINEMET CR is started. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET CR b.i.d. *Patients not receiving levodopa:* In patients with mild to moderate disease, the initial recommended dose is 1 tablet of SINEMET CR b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with 2 to 8 tablets per day, administered as divided doses at intervals ranging from 4 to 8 hours during the waking day. Higher doses (12 or more tablets per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day.

An interval of at least 3 days between dosage adjustments is recommended.

Maintenance Because Parkinson's disease is progressive, periodic clinical evaluations are recommended; adjustment of the dosage regimen of SINEMET CR may be required.

Addition of Other Antiparkinson Medications Anticholinergic agents, dopamine agonists, and amantadine can be given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added.

A dose of SINEMET (Carbidopa-Levodopa) 25-100 or 10-100 (one half or a whole tablet) can be added to the dosage regimen of SINEMET CR in selected patients with advanced disease who need additional levodopa for a brief time during daytime hours.

Interruption of Therapy Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET CR is required, especially if the patient is receiving neuroleptics. (See WARNINGS).

If general anesthesia is required, SINEMET CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED SINEMET CR 50-200 (Carbidopa-Levodopa) SUSTAINED-RELEASE TABLETS containing 50 mg of carbidopa and 200 mg of levodopa, are peach-colored, oval, scored, biconvex, compressed tablets, coded 521. They are supplied as follows:

NDC 0056-0521-68 bottles of 100

NDC 0056-0521-28 unit dose packages of 100.

Storage Avoid temperatures above 30°C (86°F). Store in a tightly closed container.

A.H.F.S. Category: 92:00 Issued June 1991 Printed in U.S.A.

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Brief Summary of 6251-3/7619403 CR-31238

TABLETS

SINEMET® (CARBIDOPA-LEVODOPA)

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS (below) and DOSAGE AND ADMINISTRATION sections in the Prescribing Information before initiating therapy.

INDICATIONS: SINEMET is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication. SINEMET is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B_6).

The incidence of levodopa-induced nausea and vomiting is less with SINEMET than with levodopa. In many patients this reduction in nausea and vomiting will permit more rapid dosage titration.

In some patients a somewhat smoother antiparkinsonian effect results from therapy with SINEMET than with levodopa. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from SINEMET.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Although the administration of carbidopa permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa. *Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, may occur at low dosages and sooner during therapy with SINEMET than with levodopa.*

Certain patients who responded poorly to levodopa have improved when SINEMET was substituted. This is most likely due to decreased peripheral decarboxylation of levodopa which results from administration of carbidopa rather than to a primary effect of carbidopa on the nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa in parkinsonian syndromes.

In considering whether to give SINEMET to patients already on levodopa who have nausea and/or vomiting, the practitioner should be aware that, while many patients may be expected to improve, some do not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing SINEMET with levodopa, about half of the patients with nausea and/or vomiting on levodopa improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

CONTRAINDICATIONS: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See DOSAGE AND ADMINISTRATION section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

PRECAUTIONS: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS (above).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

ADVERSE REACTIONS: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitation, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred.

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, protein-bound iodine, and Coombs test.

Other adverse reactions that have been reported with levodopa are: *Nervous System:* ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome. *Psychiatric:* confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria. *Gastrointestinal:* dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue. *Metabolic:* weight gain or loss, edema. *Integumentary:* malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, skin rash, loss of hair. *Genitourinary:* urinary retention, urinary incontinence, dark urine, priapism. *Special Senses:* diplopia, blurred vision, dilated pupils, oculogyric crises. *Miscellaneous:* weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

HOW SUPPLIED: Tablets SINEMET 10-100, SINEMET 25-100, and SINEMET 25-250 are supplied in bottles of 100 and unit dose packages of 100.

Storage: Tablets SINEMET 10-100 and Tablets SINEMET 25-250 must be protected from light.

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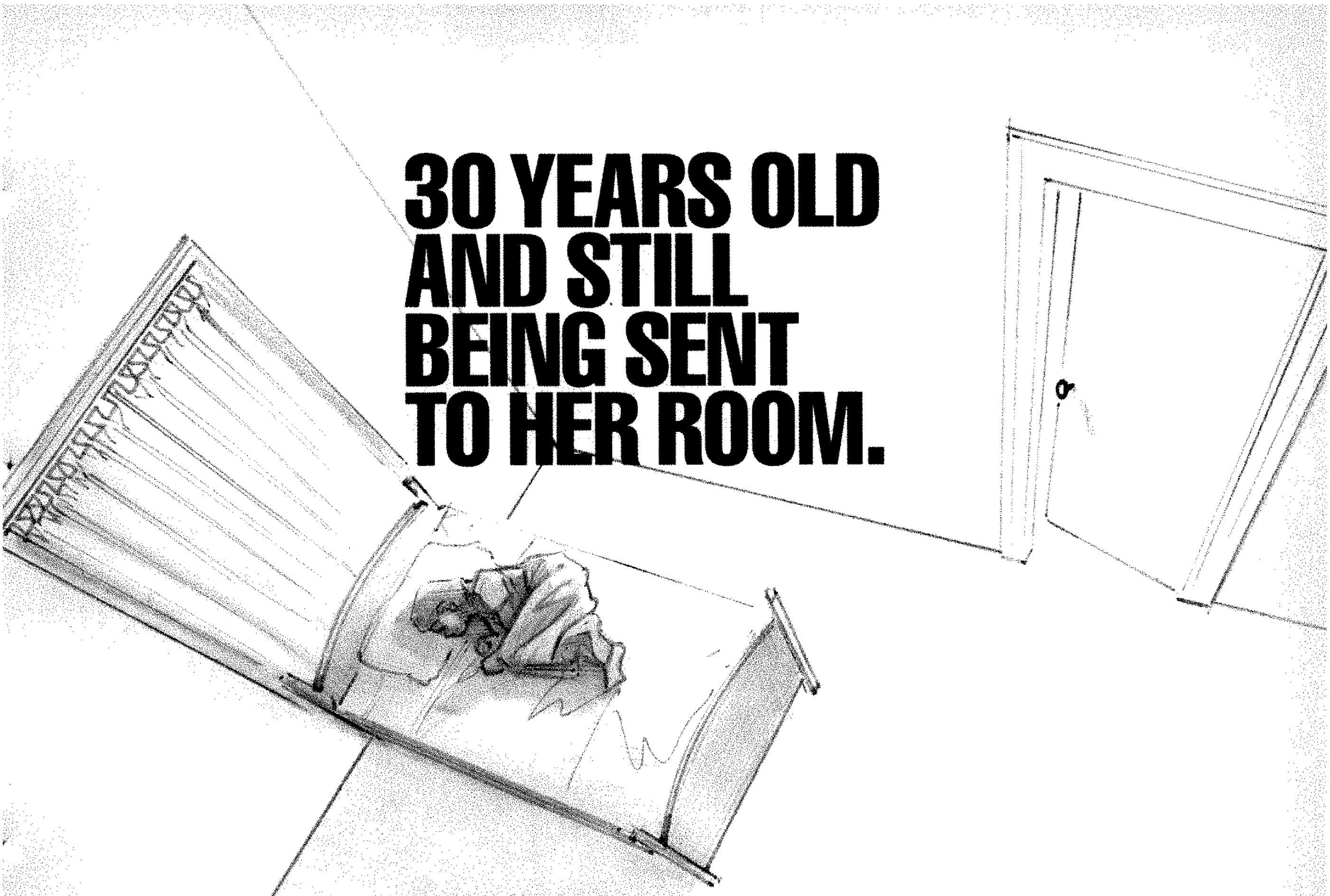
30 YEARS OLD AND STILL BEING SENT TO HER ROOM.



BY MIGRAINE.

The headaches began in her teens – and still interrupt her life without warning. A pain so intense, she confines herself to the solitude of her bedroom. She's just 1 of over 14 million Americans who live with migraine.

Stop migraine before it starts.

Abortive therapies often provide inadequate relief or cause troublesome side effects. INDERAL® LA is a once-daily *preventive* therapy that can significantly reduce the frequency and severity of common migraine.

Individualized therapy optimizes results.

Dose titration is key to successful management. Start with 80 mg/day. Increase dosage by 40 mg every two weeks to an effective dose – usually 160 mg to 240 mg daily.* Maximum dosage is 320 mg/day.

ONCE-DAILY
INDERAL® LA
(PROPRANOLOL HCl) LONG ACTING CAPSULES 60, 80, 120, 160 mg

The only once-daily migraine preventive.

INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma.

INDERAL LA should not be used during pregnancy. Patients receiving INDERAL LA sometimes experience side effects such as bradycardia, hypotension, mental depression, fatigue, bronchospasm, lupus erythematosus.

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Please see brief summary on next page.
63284

WYETH-AYERST
LABORATORIES
Philadelphia, PA 19101

INDERAL® LA (propranolol HCl) Long Acting Capsules
BRIEF SUMMARY OF PRESCRIBING INFORMATION:
CONSULT THE PACKAGE LITERATURE FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE. INDERAL LA is indicated for the following:

Management of **Hypertension** — (alone or in combination with other agents). It is not indicated for management of hypertensive emergencies.

Long-term management of **Angina Pectoris Due to Coronary Atherosclerosis.**

Migraine — for the prophylaxis of common migraine headache. It is not indicated for treatment of migraine attacks.

Management of **Hypertrophic Subaortic Stenosis** — especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS), unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Use beta blockers with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia; other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism, thus abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3, and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, tachycardia was replaced by severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Use with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity resulting in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, as both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: There was no evidence of significant drug-induced toxicity in rats or mice, employing doses up to 150 mg/kg/day over an 18-month period. There were no drug-related tumorigenic effects at any dosage levels. No impairment of fertility attributable to the drug was seen in animal reproductive studies.

PREGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Exercise caution when INDERAL (propranolol HCl) is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. The oculomucocutaneous reactions associated with practolol have not been reported with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

For management of hypertension, angina pectoris, migraine, and hypertrophic subaortic stenosis the dosage must be individualized. Usual initial dose is 80 mg once daily. **For complete dosage information see package literature.**

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

PEDIATRIC DOSAGE – At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE. INDERAL is not significantly dialyzable. If ingestion is, or may have been, recent, evacuate gastric contents, taking care to prevent pulmonary aspiration.

BRADYCARDIA: Administer atropine (0.25 to 1.0 mg); if no response to vagal blockade, administer isoproterenol cautiously. CARDIAC FAILURE: digitalization and diuretics. HYPOTENSION: vasopressors, eg, levarterenol or epinephrine (there is evidence that epinephrine is the drug of choice). BRONCHOSPASM: administer isoproterenol and aminophylline.

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on call

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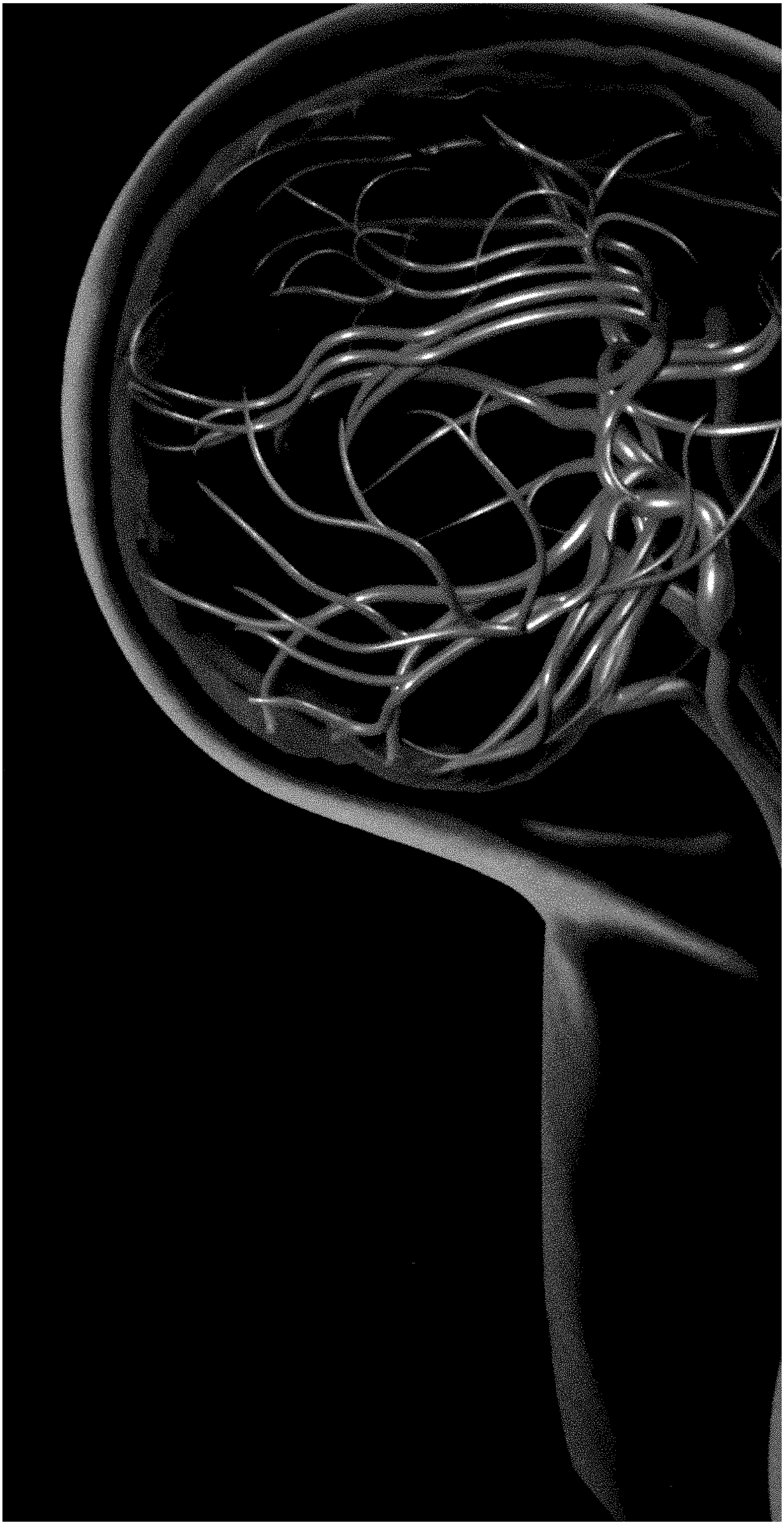
American Medical Association
Physicians dedicated to the health of America

Stroke Devastates.

Today, Significantly Reduce the Risk of Stroke.



Introducing the First Prescription Antiplatelet Agent that Significantly Reduces the Risk of Stroke[1,2]

Ticlid®
Ticlopidine HCl 250mg Tablets bid

Clinical Trials Demonstrated:

48% reduction vs aspirin[3] in risk of initial stroke in TIA[*] patients at year 1 (*P* = .0004, n = 3034), **the year of greatest risk**

33% reduction in risk[2,4] of fatal or nonfatal recurrent stroke at year 1 (*P* = .008, n = 1053), **the year of greatest risk**

Proven effective in women as well as men[1,2,3,4]

Indications

Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life threatening (see Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke

TICLID, therefore, is appropriate first-line therapy for reducing the risk of thrombotic stroke in:
- all female TIA patients
- all males at risk for recurrent stroke
- all females at risk for recurrent stroke
- all aspirin-intolerant male TIA patients

Side Effects

In clinical trials, neutropenia[†] occurred in a total of 2.4% of patients (0.8% severe[‡]) and was not typically associated with clinical signs or symptoms

Therefore, CBC monitoring (including differentials) for neutropenia is essential every 2 weeks for the first 3 months of therapy

The most frequently occurring side effects involved the GI tract: diarrhea (12.5%), nausea (7.0%), dyspepsia (7.0%); rash also occurred (5.1%)

Although most side effects were mild, 21% of patients discontinued therapy due to an adverse event in clinical trials

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[*] Analysis based on all study participants, which included patients with transient ischemic attack, transient monocular blindness, reversible ischemic neurological deficit, and minor stroke.

[†] Defined as <1200 neutrophils/mm³, seen in 50/2048 patients.

[‡] Defined as <450 neutrophils/mm³, seen in 17/2048 patients.

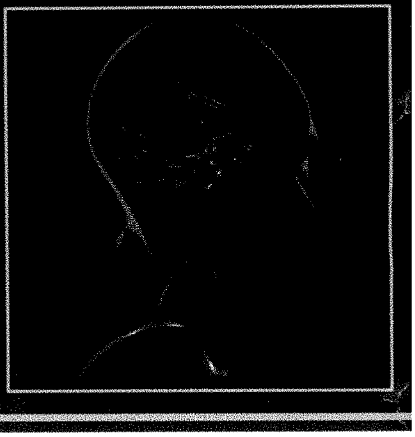
SYNTEX

1. Hass WK, Easton JD, Adams HP Jr et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med.* 1989;321(8):501-507. **2.** Gent M, Easton JD, Hachinski VC et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet.* 1989;1:1215-1220. **3.** TICLID (ticlopidine HCl) tablets full prescribing information. **4.** Biller J, Love BB, Gordon DL. Antithrombotic therapy for ischemic cerebrovascular disease. *Semin Neurol.* 1991;11(4):353-367.

Please see brief summary of prescribing information on last page.

Ticlid®

Ticlopidine HCl 250mg Tablets bid



The First Prescription Antiplatelet Agent that Significantly Reduces the Risk of Stroke

For further information, including the CBC Monitoring Program for TICLID, please call 1-800-TICLID-1.

TICLID® (ticlopidine hydrochloride) 250 mg Tablets

INDICATIONS AND USAGE TICLID is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life-threatening (See Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke. **CONTRAINDICATIONS** The use of TICLID® is contraindicated in the following conditions: Hypersensitivity to the drug. Presence of hematopoietic disorders such as neutropenia and thrombocytopenia. Presence of a hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding). Patients with severe liver impairment.

WARNINGS

Neutropenia

Neutropenia defined in these studies as an ANC <1200 neutrophils/mm^3 occurred in 50 of 2,048 (2.4%) stroke patients who received TICLID in clinical trials. *Severe Neutropenia (<450 neutrophils/mm^3)*: Severe neutropenia and/or agranulocytosis occurred in 17 of the 2,048 (0.8%) patients who received TICLID. When the drug was discontinued in these patients, the neutrophil counts returned to normal (>1200 neutrophils/mm^3) within 1-3 weeks. *Mild to Moderate Neutropenia (451-1200 neutrophils/mm^3)*: Mild to moderate neutropenia occurred in 33 of the 2,048 (1.6%) patients who received TICLID. Eleven of the patients discontinued treatment and recovered within a few days. In the remaining 22 patients, the neutropenia was transient and did not require discontinuation of therapy. The onset of severe neutropenia occurred 3 weeks to 3 months after the start of therapy with TICLID, with no documented cases of severe neutropenia beyond that time in the large controlled trials. The bone marrow typically showed a reduction in myeloid precursors. It is therefore essential that CBCs and white cell differentials be performed every two weeks starting from the second week to the end of the third month of therapy with TICLID, but more frequent monitoring is necessary for patients whose absolute neutrophil counts have been consistently declining or are 30% less than the baseline count. Neutropenia (an absolute neutrophil count (ANC) of less than 1200 neutrophils/mm^3) is calculated as follows: ANC = WBC × % neutrophils. If clinical evaluation and repeat laboratory testing confirm the presence of neutropenia (<1200/mm^3), the drug should be discontinued. In clinical trials, when therapy was discontinued immediately upon detection of neutropenia, the neutrophil counts returned to normal within 1-3 weeks. After the first three months of therapy, CBCs need be obtained only for patients with signs or symptoms suggestive of infection.

Thrombocytopenia Rarely, thrombocytopenia may occur in isolation or together with neutropenia. If clinical evaluation and repeat laboratory testing confirm the presence of thrombocytopenia (<80,000 cells/mm^3), the drug should be discontinued. Cholesterol Elevation TICLID® therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8-10% within one month of therapy and persist at that level. The ratios of the lipoprotein subfractions are unchanged. **Other Hematological Effects** Rare cases of pancytopenia and thrombotic thrombocytopenic purpura, some of which have been fatal, have been reported in Post-Marketing Surveillance. **Anticoagulant Drugs** The tolerance and safety of coadministration of TICLID with heparin, oral anticoagulants, or fibrinolytic agents has not been established. If a patient is switched from an anticoagulant or fibrinolytic drug to TICLID, the former drug should be discontinued prior to TICLID administration. **PRECAUTIONS General** TICLID should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or pathological conditions. If it is desired to eliminate the antiplatelet effects of TICLID prior to elective surgery, the drug should be discontinued 10-14 days prior to surgery. Several controlled clinical studies have found increased surgical blood loss in patients undergoing surgery during treatment with ticlopidine. In TASS and CATS it was recommended that patients have ticlopidine discontinued prior to elective surgery. Several hundred patients underwent surgery during the trials, and no excessive surgical bleeding was reported. Prolonged bleeding time is normalized within two hours after administration of 20 mg methylprednisolone i.v. Platelet transfusions may also be used to reverse the effect of TICLID on bleeding. **GI Bleeding** TICLID prolongs template bleeding time. The drug should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients on TICLID. (See Contraindications.) **Use in Hepatically Impaired Patients** Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of TICLID is not recommended in this population. (See Clinical Pharmacology and Contraindications.) **Use in Renally Impaired Patients** There is limited experience in patients with renal impairment. In controlled clinical trials, no unexpected problems have been encountered in patients having mild renal impairment and there is no experience with dosage adjustment in patients with greater degrees of renal impairment. Nevertheless, for renally impaired patients it may be necessary to reduce the dosage of ticlopidine or discontinue it altogether, if hemorrhagic or hematopoietic problems are encountered. (See Clinical Pharmacology) **Information for the Patient (See PPI)** Patients should be told that a decrease in the number of white blood cells (neutropenia) can occur with TICLID® especially during the first three months of treatment, and that if neutropenia is severe, it could result in an increased risk of infection. They should be told it is critically important to obtain the scheduled blood tests to detect neutropenia. Patients should also be reminded to contact their physicians if they experience any indication of infection such as fever, chills, and sore throat, all of which may be consequences of neutropenia. All patients should be told that it may take them longer than usual to stop bleeding when they take TICLID and that they should report any unusual bleeding to their physician. Patients should tell physicians and dentists that they are taking TICLID before any surgery is scheduled and before any new drug is prescribed. Patients should be told to report promptly side effects of TICLID such as severe or persistent diarrhea, skin rashes, or subcutaneous bleeding, or any signs of cholestasis, such as yellow skin or sclera, dark urine, or light colored stools. Patients should be told to take TICLID with food or just after eating in order to minimize gastrointestinal discomfort. **Laboratory Tests** *Liver Function:* TICLID therapy has been associated with elevations of alkaline phosphatase and transaminases which generally occurred within 1-4 months of therapy initiation. In controlled clinical trials, the incidence of elevated alkaline phosphatase (greater than 2 times upper limit of normal) was 7.6% in ticlopidine patients, 6.0% in placebo patients and 2.5% in aspirin patients. The incidence of elevated AST (SGOT) (greater than 2 times upper limit of normal) was 3.1% in ticlopidine patients, 4.0% in placebo patients and 2.1% in aspirin patients. No progressive increases were observed in closely monitored clinical trials (e.g. no transaminase greater than 10 times the upper limit of normal was seen), but most patients with these abnormalities had therapy discontinued. Occasionally patients had developed minor elevations in bilirubin. Based on post-marketing and clinical trials experiences, liver function testing should be considered whenever liver dysfunction is suspected, particularly during the first four months of treatment. **Drug Interactions** Therapeutic doses of TICLID caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios, or being given to patients with hepatic impairment, may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine. Studies of specific drug interactions yielded the following results: ***Aspirin:*** Aspirin did not modify the ticlopidine-mediated inhibition of ADP-induced platelet aggregation, but ticlopidine potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of this combination has not been established and concomitant use of aspirin and ticlopidine is not recommended. (See Precautions -- GI Bleeding). ***Antacids:*** Administration of TICLID after antacids resulted in an 18% decrease in plasma levels of ticlopidine. ***Cimetidine:*** Chronic administration of cimetidine reduced the clearance of a single dose of TICLID by 50%. ***Digoxin:*** Co-administration of TICLID with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected. ***Theophylline:*** In normal volunteers, concomitant administration of TICLID resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hr and a comparable reduction in total plasma clearance of theophylline. ***Phenobarbital:*** In six normal volunteers, the inhibitory effects of TICLID on platelet aggregation were not altered by chronic administration of phenobarbital. ***Phenytoin:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID and it may be useful to remeasure phenytoin blood concentrations. ***Propranolol:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID.

℞ ______

TICLID 250 mg
#30
Sig: 1 Tab bid
with meals

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, TICLID was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs without evidence of clinically significant adverse interactions. (See Precautions.) **Food Interaction:** The oral bioavailability of ticlopidine is increased by 20% when taken after a meal. Administration of TICLID with food is recommended to maximize gastrointestinal tolerance. In controlled trials, TICLID was taken with meals. **Carcinogenesis, Mutagenesis, Impairment of Fertility** In a two-year oral carcinogenicity study in rats, ticlopidine at daily doses of up to 100 mg/kg (610 mg/m^2) was not tumorigenic. For a 70 kg person (1.73m^2 body surface area), the dose represents 14 times the recommended clinical dose on a mg/kg basis and 2 times the clinical dose on body surface area basis. In a 78 week oral carcinogenicity study in mice ticlopidine at daily doses up to 275 mg/kg (1180 mg/m^2) was not tumorigenic. The dose represents 40 times the recommended clinical dose on a mg/kg basis and 4 times the clinical dose on body surface area basis. Ticlopidine was not mutagenic in *in vitro* Ames test, rat hepatocyte DNA-repair assay, and Chinese hamster fibroblast chromosomal aberration test and *in vivo* mouse spermatozoid morphology test, Chinese hamster micronucleus test and Chinese hamster bone marrow cell sister chromatid exchange test. Ticlopidine was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day. **Pregnancy: Teratogenic Effects** Pregnancy Category B. Teratology studies have been conducted in mice (doses up to 200 mg/kg/day), rats (doses up to 400 mg/kg/day) and rabbits (doses up to 200 mg/kg/day). Doses of 400 mg/kg in rats, 200 mg/kg/day in mice, and 100 mg/kg in rabbits produced maternal toxicity as well as fetal toxicity, but there was no evidence of a teratogenic potential of ticlopidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers** Studies in rats have shown ticlopidine is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ticlopidine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** Safety and efficacy in patients under the age of 18 have not been established. **Geriatric Use** Clearance of ticlopidine is somewhat lower in elderly patients and trough levels are increased. The major clinical trials with TICLID were conducted in an elderly population with an average age of 64 years. Of the total number of patients in the therapeutic trials, 45% of patients were over 65 years old and 12% were over 75 years old. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse reactions were relatively frequent, with over 50% of patients reporting at least one. Most (30 to 40%) involved the gastrointestinal tract. Most adverse effects are mild, but 21% of patients discontinued therapy because of an adverse event, principally diarrhea, rash, nausea, vomiting, G.I. pain, and neutropenia. Most adverse effects occur early in the course of treatment, but a new onset of adverse effects can occur after several months. The incidence rates of adverse events listed in the following table were derived from multicenter, controlled clinical trials described above comparing TICLID, placebo, and aspirin over study periods of up to 5.8 years. Adverse events considered by the investigator to be probably drug-related that occurred in at least one percent of patients treated with TICLID are shown in the following table:

Percent of Patients with Adverse Events in Controlled Studies

Event	TICLID (n = 2048) Incidence	Aspirin (n = 1527) Incidence	Placebo (n = 536) Incidence
Any Events	*60.0(20.9)*	*53.2(14.5)*	*34.3 (6.1)*
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	1.7 (0.9)
Dyspepsia	7.0 (1.1)	9.0 (2.0)	0.9 (0.2)
Rash	5.1 (3.4)	1.5 (0.8)	0.6 (0.9)
GI Pain	3.7 (1.9)	5.6 (2.7)	1.3 (0.4)
Neutropenia	2.4 (1.3)	0.8 (0.1)	1.1 (0.4)
Purpura	2.2 (0.2)	1.6 (0.1)	0.0 (0.0)
Vomiting	1.9 (1.4)	1.4 (0.9)	0.9 (0.4)
Flatulence	1.5 (0.1)	1.4 (0.3)	0.0 (0.0)
Pruritus	1.3 (0.8)	0.3 (0.1)	0.0 (0.0)
Dizziness	1.1 (0.4)	0.5 (0.4)	0.0 (0.0)
Anorexia	1.0 (0.4)	0.5 (0.3)	0.0 (0.0)
Abnormal Liver Function test	1.0 (0.7)	0.3 (0.3)	0.0 (0.0)

Incidence of discontinuation, regardless of relationship therapy, is shown in parentheses

Neutropenia/Thrombocytopenia See Warnings. **Gastrointestinal** TICLID therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and typically are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. **Hemorrhagic** TICLID has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding and perioperative bleeding. Intracerebral bleeding was rare in clinical trials with TICLID, with an incidence no greater than that seen with comparator agents. (Ticlopidine 0.5%, aspirin 0.6%, placebo 0.75%.) **Rash** Ticlopidine has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean onset time of 11 days. If drug is discontinued, recovery occurs within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of severe rashes. **Less Frequent Adverse Reactions (Probably Related)** Clinical adverse experiences occurring in 0.5 to 1.0 percent of patients in the controlled trials include: Digestive System: GI fullness. Skin and Appendages: urticaria. Nervous System: headache. Body as a Whole: asthenia, pain. Hemostatic System: epistaxis. Special Senses: tinnitus. In addition, rarer, relatively serious events have also been reported, mainly from foreign post marketing experience: Pancytopenia, hemolytic anemia with reticulocytosis, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, cholestatic jaundice, nephrotic syndrome, myositis, hyponatremia, immune thrombocytopenia and thrombocytopenic thrombotic purpura (TTP). **OVERDOSAGE** One case of deliberate overdosage with TICLID has been reported by foreign postmarketing surveillance program. A 38 year old male took a single 6000 mg dose of TICLID (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Single oral doses of ticlopidine at 1600 mg/kg and 500 mg/kg were lethal to rats and mice, respectively. Symptoms of acute toxicity were GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and abnormal gait. **DOSAGE AND ADMINISTRATION** The recommended dose of TICLID is 250 mg BID taken with food. Other doses have not been studied in controlled trials for these indications.

SYNTEX
SYNTEX LABORATORIES, INC.
PALO ALTO, CA 94304

U.S. Patent Nos. 4,051,141; 4,591,592
02-0431-00-00 NOVEMBER 1991
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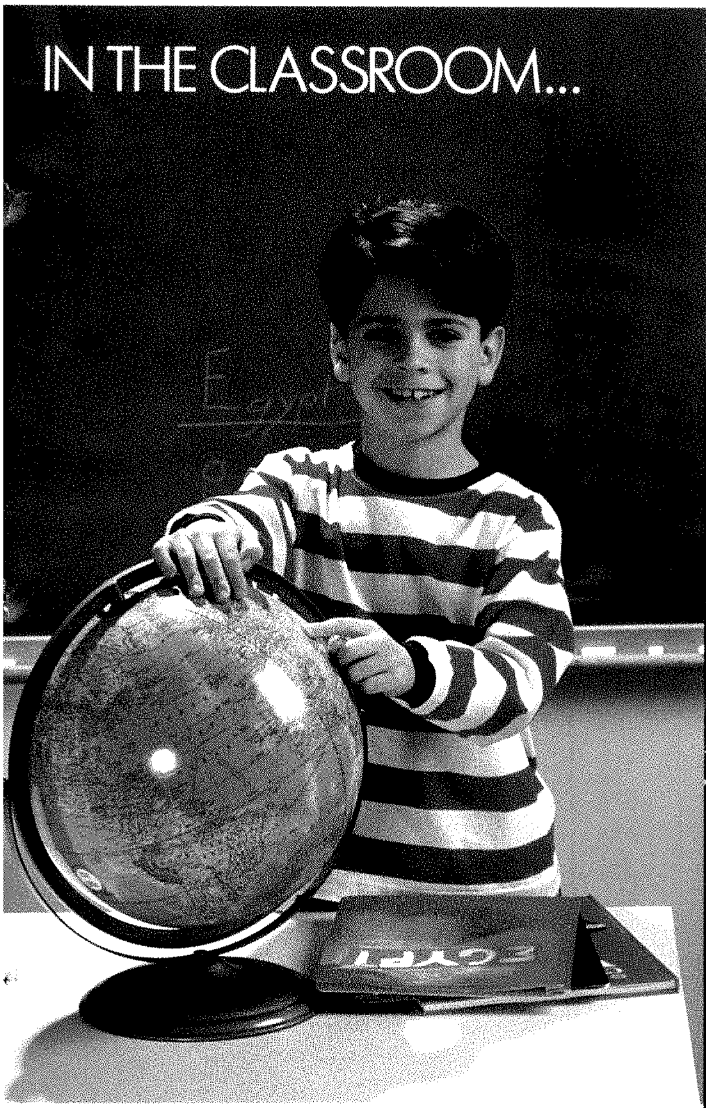
Seizures controlled, thoughts clear, smiles bright


IN THE CLASSROOM...

Low risk of cognitive impairment[1]

Generally avoids hirsutism[2,3]

Avoids gingival hyperplasia[2,3]

BASEL

© 1992, CIBA-GEIGY Corporation 318-21251-A 4

Tegretol® 200 mg scored tablets
100 mg chewable tablets

carbamazepine USP

... because after seizure control, there's a lot of living to do!

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the next page, especially the boxed warning.

References:

1. Smith DB, Mattson RH, Cramer JA et al. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia*. 1987;28(suppl 3):S50-S58.
2. Mattson RH, Cramer JA, Collins JF et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med*. 1985;313:145-151.
3. Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsia*. 1988;29:794-804.

Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg—red-speckled, pink
Tablets of 200 mg—pink
Suspension of 100 mg/5 ml

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

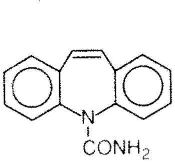
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, and as a suspension of 100 mg/5 ml (teaspoon). Its chemical name is 5*H*-dibenz[b,f]azepine-5-carboxamide, and its structural formula is:



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Tablets: Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

In clinical studies both suspension and conventional tablet delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster than the tablet. Following a b.i.d. dosage regimen, the suspension has higher peak levels and lower trough levels than those obtained from the tablet formulation for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4 to 5 hours after administration of oral tablets. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

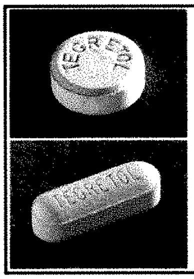
1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.



Only TEGRETOL brand of carbamazepine, provides the prescribing flexibility of a 100-mg scored chewable tablet, as well as a 200-mg scored tablet.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10,11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid, fluoxetine or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of

6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: Either 200 mg b.i.d. for tablets or 1 teaspoon q.i.d. for suspension (400 mg per day). Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: Either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension (200 mg per day). Increase at weekly intervals by adding up to 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg/daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100 .... NDC 58887-052-30
Unit Dose (blister pack)
  Box of 100
  (strips of 10) .... NDC 58887-052-32

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

  Bottles of 100 .... NDC 58887-027-30
  Bottles of 1000 .... NDC 58887-027-40
Unit Dose (blister pack)
  Box of 100
  (strips of 10) .... NDC 58887-027-32

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture. Dispense in tight container (USP).

Suspension 100 mg/5 ml (teaspoon)—yellow-orange, citrus-vanilla flavored

  Bottles of 450 ml .... NDC 58887-019-76

Shake well before using.
Do not store above 86°F.
Dispense in tight, light-resistant container (USP).

Printed in U.S.A. C91-50 (Rev. 11/91)

BASEL Pharmaceuticals

BASEL Pharmaceuticals
Division of
CIBA-GEIGY Corporation
Summit, New Jersey 07901

Dosage Information: Tablets and Suspension

Indication	Initial Dose		Subsequent Dose		Maximum Dose
	Tablet	Suspension	Tablet	Suspension	Tablet or Suspension
Epilepsy					
6-12 years of age	100 mg b.i.d. (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 100 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 1 teaspoon (100 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours
Over 12 years of age	200 mg b.i.d. (400 mg/day)	1 teaspoon q.i.d. (400 mg/day)	Add up to 200 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 2 teaspoons (200 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours: 12-15 years 1200 mg/24 hours: over 15 years 1600 mg/24 hours: adults, in rare instances
Trigeminal Neuralgia	100 mg b.i.d. on the first day (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 200 mg per day in increments of 100 mg every 12 hours	Add up to 2 teaspoons (200 mg) per day q.i.d.	1200 mg/24 hours

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Calender of Meetings

June

9-14	Seventh International Symposium on the Facial Nerve, Cologne, Germany. Contact Congress Secretary, Klinik und Poliklinik für HNO, Universität zu Köln, Kongressbüro, Joseph Stelzmann Strasse 9, D-5000 Köln, Germany.
14-21	32nd International Neuropsychiatric Gerald Grinschgl Symposium, Graz, Austria. Contact Professor Helmut Lechner, University Department of Neurology, Auenbruggerplatz 22, 8036 Graz, Austria.

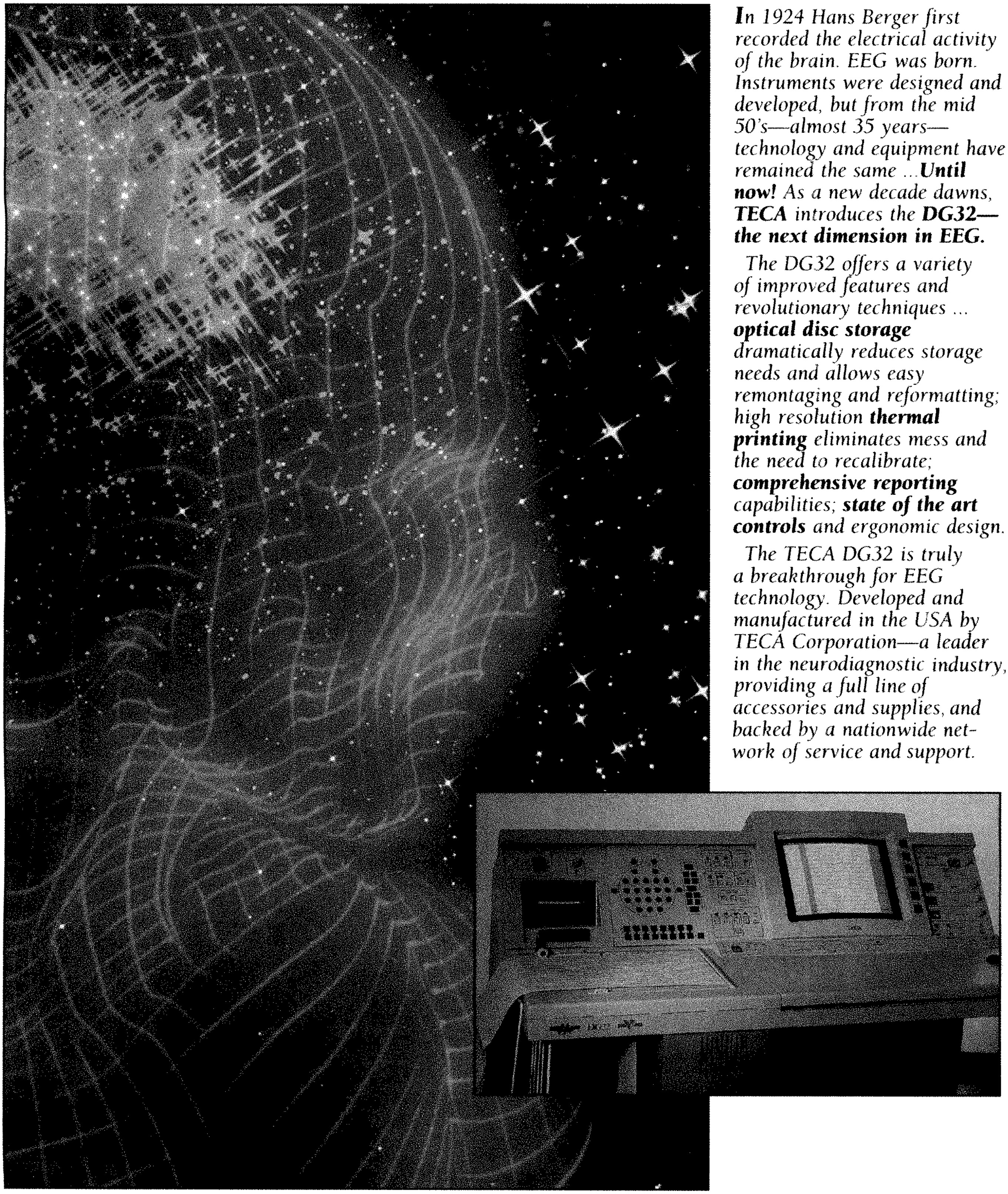
September

2-4	Second International Conference on Ultrasound Angiography, Southampton, England. Contact Conference Secretariat, Ultrasound Angiography, PO Box 15, Eastleigh, England S05 5XG.
6-9	Conference on the Melanotropic Peptides, Rouen, France. Contact Conference Department, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212) 838-0230.
8-12	Second World Congress of the International Stroke Society, Washington, DC. Contact Convention Office, Bowman Gray School of Medicine of Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157-1074; (919) 748-6103.
19-20	Annual Meeting of the American Electroencephalographic Society, San Francisco, Calif. Contact Jacquelyn T. Coleman, Executive Director, American Electroencephalographic Society, PO Box 30, Bloomfield, CT 06002; (203) 243-3977.
19-24	Sixth European Congress on Clinical Neurophysiology, Lisbon, Portugal. Contact Secretariat, Laboratory EMG/EEG, Hospital de Santa Maria, 1699 Lisbon Codex, Portugal.
22-25	First International Symposium on Brain Death, Havana, Cuba. Contact Palacio de las Convenciones, Apartado 16046, Havana, Cuba.
23-26	66th Annual Meeting of the American Thyroid Association, Mayo Civic Center, Rochester, Minn. Contact American Thyroid Association, Walter Reed Army Medical Center, Washington, DC 20307-5001; (202) 882-7717.

October

4-5	Second International Congress on Evaluation Methods in Rehabilitation Medicine, Montreal, Quebec. Contact Pierrette Boivin, 6300 Darlington St, Montreal, Quebec, Canada H3S 2J4; (514) 340-2089.
8-10	American Association of Neuroscience Nurses Midannual Meeting, Newport, RI. Contact American Association of Neuroscience Nurses, 224 N Des Plaines St, Suite 601, Chicago, IL 60661; (312) 993-0043.
10-15	15th Brazilian Congress of Neurology, Porto Alegre, Brazil. Contact Plenarium, Ramiro Barcelos, 820, 90210 Porto Alegre, Brazil.

TECA DG32 *Redefining the shape of EEG*



*In 1924 Hans Berger first recorded the electrical activity of the brain. EEG was born. Instruments were designed and developed, but from the mid 50's—almost 35 years—technology and equipment have remained the same ... **Until now!** As a new decade dawns, **TECA** introduces the **DG32—the next dimension in EEG.***

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Violent Brain Injuries by Gunshot in Duval County, Florida, 1989-1991

To the Editor.—In response to the editorial on "violence" in the November 1991 issue of the ARCHIVES, the last 3 years' data (1989 through 1991) on violent brain injuries by gunshot were reviewed and analyzed from the Trauma Registry of the University Medical Center of Jacksonville, Duval County, Florida. University Medical Center is the only Trauma One medical facility in Duval County and surrounding northeast Florida and southeast Georgia. It serves about 600 000 people in Jacksonville, and 1.2 million people in 20 counties of northeast Florida and southeast Georgia. This is not a "high crime" area. Therefore, these data reflect the incidence of violent brain injuries for this entire region.

This search was limited to assault by firearms and explosives, E code E965. A total of 107 patients suffered from violent brain injuries by gunshot in the last 3 years (1989 through 1991). There were three subgroups in this E code: (1) E965.0, assault by handguns, pistol, or revolver, 24 patients (22.43%); (2) E965.2, assault by hunting rifle, three patients (2.80%); and (3) E965.4, assault by unspecified firearms, 80 patients (74.77%). The number of gunshot-induced brain injuries was 36 (33.64%) in 1989, 41 (38.32%) in 1990, and 30 (28.04%) in 1991.

Of 107 patients, 90 (84.11%) were male and 17 (15.89%) were female. Analysis of racial distribution showed 67 (62.62%) blacks, 38 (35.51%) whites, and two (1.87%) Hispanics. Most of the brain injuries occurred in the age group of 15 to 45 years. Analysis of initial emergency department disposition revealed 37 (34.58%) died, 33 (30.84%) were admitted to the operating room, 17 (15.89%) were admitted to an intensive care unit, and 20 (18.69%) were admitted to the hospital inpatient service. The final disposition from acute care revealed 58 (54.21%) died, 41 (38.32%) were discharged home, six (5.61%) were referred to an inpatient rehabilitation facility, one (0.93%) was referred to a nursing facility, and one (0.93%) was referred to another acute care facility. Out of the 58 patients who finally died, 45 (77.5%) had an admission Glasgow Coma Scale (GCS) of 3 to 4, 11 (18.9%) patients had a GCS of 5 to 13, and only two patients had a GCS of 14 to 15. The admission GCS was a fairly accurate predictor of the final outcome.

The final functional outcome was reflected in the analysis of functional independence in self-feeding, locomotion, and linguistic expression. Forty-two (39.25%) achieved independence in self-feeding, 28 (26.17%) independence in walking without assistive devices, 14 (13.08%) walking with assistive devices, and 42 (39.25%) achieved independence in linguistic expressions, including verbalization or writing of complex and abstract ideas. Analysis of drug testing showed that in 97 (90.65%) patients drug testing was either not done or the results were not known. The drugs detected were cocaine in four patients and a benzodiazepine in one patient.

A few comparable studies of civilian gunshot injuries of the brain have been reported.[1-8] Levi et al[1] report 31 cases of penetrating craniocerebral injuries in civilians during a 6-year period (1984 through 1989). It is a much lower incidence than our series of 107 cases in 3 years. They report a 58% mortality, which is comparable to our 54.21% mortality. They report an invariably fatal outcome in patients with an admission GCS of 3 or 4. In our series, the mortality in patients with a GCS of 3 to 4 was 77.5%. Benzel et al[2] report a mortality of 56% in their series of 120 civilian gunshot injury cases. Siccardi et al[3] report a 84.7% mortality within 3 hours of injury in a large series of 314 civilian patients. Mancuso et al[4] report 40 cases in 8 years in their series. They also report very poor prognosis in patients with a GCS of 3 to 4. Cavaliere et al[5] report a series of 178 cases of civilian brain injuries with 88% mortality within 3 hours after injury. Clark et al[6] report an analysis of 76 cases of civilian brain gunshot injuries during a 20-month period. They report a mortality of 62% with invariable fatality in patients with a GCS of 3. The data from our present study are comparable to the above published reports.

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1964

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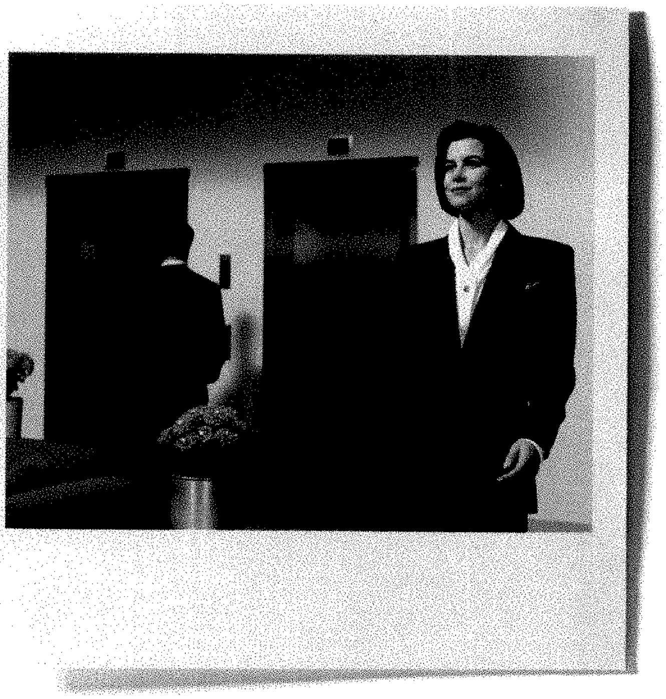

A proven combination for the symptom complex of tension headache, including the pain-relieving potency of codeine.

FIORINAL® WITH CODEINE CAPSULES CIII

Please see brief summary of prescribing information on following page.

(Each capsule contains: codeine phosphate 30 mg; [Warning: May be habit-forming]; butalbital 50 mg; [Warning: May be habit-forming]; caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

SANDOZ

SANDOZ PHARMACEUTICALS CORPORATION
EAST HANOVER, NEW JERSEY 07936

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FWC-0192-01 2/92

BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE CIII CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming], butalbital USP, 50 mg [warning: may be habit forming], caffeine USP, 40 mg, aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiorinal® with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	**Fiorinal®/Codeine (N = 382)**	**Placebo (N = 377)**
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caused by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® with Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorinal® with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overdosage is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion, and coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus; hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restlessness, tremor and delirium; tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® with Codeine. However, because strategies for the management of an overdose continually evolve, consultation with a regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g

Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)

Caffeine: toxic dose greater than 1.0 g; lethal dose unknown

Codeine: lethal dose 0.5-1.0 g (adult)

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[NOVEMBER 1, 1990 FWC-Z26]

Make My Day

I live in a moderately sized city in upstate New York. It is conservative by usual standards. George Eastman, the industrialist and great benefactor, noted that it was a nice place to raise children. It has broad streets, nice parks, many cultural opportunities, good music, excellent medical care, and over 60 homicides a year. Two years ago we had a serial killer who brutally murdered over a dozen women. This is a city that prides itself in addressing problems by concerned citizen groups. Maybe these groups have been effective; maybe without them we would have had 100 homicides a year.

A very disquieting note is our reaction to this. In the morning paper you read about another homicide, and turn to the sports page to see what happened to the Bills. We are jaded. We have lost our sense of outrage. We suffer from violence overload. Now almost no one talks about the 66 (or was it 67 or 68?) homicides last year, or the 13 (no I think it was 14) murders by Arthur Shawcross. There is violence or aggressive behavior everywhere. Arnold, Clint, and Charles dispatch half the male population of the United States in every new picture. Admittedly, they are on the side of justice. I was driving down the road observing the speed limit, a defect in my personality occasionally manifesting itself, and was passed by an attractive, but impatient, woman, who shot me a finger in payment for my rectitude. On her rear bumper there was a sticker that read, "To Know Me Is To Love Me" (I wonder). My car, my beloved Jeep, was stolen a few weeks ago and was turned up by the police completely wrecked. My first reaction was to ask what might have happened to the occupants, but I am too embarrassed to say what I thought.

Violent and aggressive behavior is a social, educational, housing, legal, and health issue. We see it in others and we see it in ourselves. For example, the brusque handling of a patient is an aggressive act. Aggressive in that we react against someone who turns to us at their most vulnerable time.

The American Medical Association is addressing the issue of violence with the theme issue of the *Journal of the American Medical Association* and with articles in its specialty journals. The ARCHIVES is presenting four articles and a letter to the editor on this theme of special interest to our specialty. The first, by Dr Menken,[1] emphasizes the failure of our present educational system to help students understand the issues associated with violent and aggressive behavior. The second is by Elliott,[2] a neurologist, who has had wide experience in dealing with "the violent few." He points out the importance of biological factors in certain forms of violent behavior. Mahowald et al[3] look at the elusive problem of violence and sleep behavior. Ciccone,[4] a leader in the field of forensic psychiatry, describes the role of the specialist as an expert witness in cases involving violence. Finally, Deshmukh et al[5] chronicle their experience with gunshot wounds.

Neurologists have a special role to play in violence. As citizens we must necessarily have concern for this plague. As physicians we must become more aware of the problem and educate our patients and the public about this serious health problem. As neurologists we are particularly equipped to diagnose and treat these problems when they have a biological basis.

ROBERT J. JOYNT, MD, PHD
Chief Editor

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Grappling With the Enigma of Violence

An Educational Approach

Matthew Menken, MD

As we approach the end of a millennium, it is appropriate that neurologists and other physicians link forces with the public in asking what improvements we want to achieve in health care, and how this can be done. Early in the 20th century, the population of the United States consisted mainly of children and young adults. In 1900, life expectancy at birth was 46.6 years and 48.7 years for white males and females, compared with only 32.5 years and 33.5 years for black males and females. Medical care of that period focused on acute, life-threatening illnesses, was usually ineffective, and was relatively inexpensive. Priority setting and resource allocation were not relevant issues. During the first half of this century, death rates from such disorders as diphtheria, scarlet fever, tuberculosis, pertussis, and rubeola plummeted, continuing a downward trend that started during the second half of the 19th century. This trend was largely due to the improved socioeconomic and educational status of the population, public health measures, immunizations, and the development of effective treatments. By 1950, life expectancy at birth was 66.5 years and 72.2 years for white males and females, and 58.9 years and 62.7 years for black males and females.[1]

As there is no evidence that socioeconomic factors or medical research has been able to prolong the optimum life expectancy of humans, it is understandable that life expectancy at birth has increased more slowly in recent years. As of 1989, life expectancy at birth for white males and females was 72.6 years and 79.1 years; and for black males and females, 65.2 years and 74.0 years. A life span greater than 100 years remains as elusive as ever. At the present time, chronic illness, especially among the elderly, and a variety of disorders that collectively reflect individual behavior and sociocultural values consume a major portion of our total professional effort, and society's costs.[2] Given that the resources that can be devoted to health care are always finite in the face of seemingly infinite demand, it has become evident that every society needs to identify its major health problems and to focus preventive and therapeutic efforts on them.

While we correctly call attention to the many scientifically approved and important research projects that are not carried out each year because of a lack of funding, it is also clear that not every worthy objective can be a priority, since priorities are meaningless if they include everything. For example, the Secretary of State for Health in the United Kingdom has proposed three criteria for selecting health priority areas: areas for which improvements in the health of the nation are most likely; areas for which strategies for targeted improvement in health status can be monitored; and areas for research that may increase the scope of national health priorities and targets. Using these criteria, 16 priority areas have been identified, including selected causes of substantial morbidity and mortality (stroke, trauma, and mental health), factors that contribute to these causes of morbidity and mortality (tobacco and alcohol), and areas of potential improvement or regression of national health status in the foreseeable future (rehabilitation, acquired immunodeficiency syndrome, and additional vaccines to prevent communicable diseases).[3]

VIOLENCE AS A HEALTH PRIORITY

Using criteria grounded on a population perspective, it is eminently clear that violence is currently a priority health problem in the United States, where the homicide rate alone is three to eight times higher than in other Western democracies.[4] As in the case of cocaine-related emergency department episodes, the lamentable problem of violence is greatest among minority youth and young adults. Homicides claimed 22 000 lives in the United States in 1988, and was the leading cause of death among black males in the 15- to 34-year-old age group. More than half of all homicide victims in the United States between 1986 and 1989 were in this age group, of whom about two thirds were murdered with a handgun or some other kind of firearm.[1] During the 1980s, more than 11 000 high school students died as a result of homicides with firearms. Even younger children are not infrequently affected. As a recent heartbreaking example, an 11-year-old boy, while playing in his New York City apartment less than 2 weeks before Christmas, shot his 9-year-old friend in the abdomen with his brother's .45-caliber semiauto-

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From the World Federation of Neurology Research Group on Neurological Education and the Departments of Medicine and Neurology, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, New Brunswick.

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matic weapon, believing it to be a toy; when called to the scene, the police recovered 200 vials of "crack" cocaine from the closet where the boy had discovered the gun (*The New York Times*. December 16, 1991:B2).

In the 1990 national school-based Youth Risk Behavior Survey, it was estimated that nearly 20% of all students in grades 9 through 12 carried a weapon at least once in the month preceding the survey, during which time there were an astonishing 71 weapon-carrying incidents per 100 students.[5] Just as alcohol is a contributing factor in roughly 25% of all road traffic accidents, so a range of drugs (both legally prescribed and deliberately misused), often combined with alcohol, contribute to homicides and suicides. In 1980, a Public Health Service national health objective called for a reduction of the death rate from homicide among black males aged 15 to 24 years from 70.7 homicides per 100 000 (as of 1978) to below 60 per 100 000 by 1990.[6] However, in 1988, there were 101.8 deaths per 100 000 in this age group, an increase of 44% in just one decade.

The dramatic increase in societal violence since World War II appears difficult to understand and virtually impossible to contain. There are more than 20 000 laws in the United States that deal with the sale, distribution, and use of firearms, without convincing evidence of effectiveness. Since studies of deaths in the home due to firearms show that such events are only rarely related to use of weapons in self-defense, and are 40 times more likely to be the result of accidents, suicides, and homicides, some have called for physicians to adopt a leadership role in persuading their patients and the public of the need for still further legislation to ban the private use of handguns altogether.[7] Although such proposals clearly merit our vigorous support, the failure of recent legislation to control illicit drug availability and abuse, especially among those racial and ethnic groups most affected, together with a dramatic decline in tobacco consumption in recent years that is largely unrelated to legislation, suggests that educational approaches may also be helpful. In the discussion that follows, the remedial steps proposed are directed at the problem of violence in and out of schools among our nation's youth, especially minority children and young adults. I approach this topic with the bias that educational measures are, almost always, greatly to be preferred to punitive proposals in dealing with grave and complex social issues, based in part on my activities with the World Federation of Neurology Research Group on Neurological Education.[8]

AN EDUCATIONAL MANIFESTO

Mark Twain is reputed to have said that the ancients stole all of our best ideas from us. In this context, when a prestigious study identified and examined the 102 most important ideas in *The Great Books of the Western World* in 1952,[9] violence was not included as an element of the core vocabulary of philosophical or human thought, distinct from its incorporation among such concepts as war, tyranny, good and evil, life and death, and punishment. However, when the author of the 1952 study of great ideas revisited this topic about 30 years later, he included violence among an abridged list of 64 core philosophical concepts in the great books collection.[10] Clearly, violence appears to be moving up in the lexicon of philosophically important issues, concomitant with its intrusion into all aspects of life in our society.

In my view, it is not surprising that the United States has experienced a much greater problem of violence among its youth than many other Western nations. I suggest that Draconian prison sentences and the best efforts of those who provide social services (including medical care) will probably not be much more effective in the future than they have been in the recent past, unless they are accompanied by fundamental reform of our educational system. Between 1980 and 1990, the inmate population in New Jersey's prisons increased from 86.9 to 282.5 inmates per 100 000 population, or 225%. This is not to suggest that efforts by society to prevent violence; to protect those threatened or injured; to punish those guilty of heinous crimes against their fellow human beings; and to provide a full range of diagnostic, therapeutic, and rehabilitative services to victims and perpetrators alike should not be expanded. Clearly, such deterrent and compensatory measures have the capacity to make a difference under some circumstances.

When viewed from the perspective of the World Federation of Neurology Research Group on Neurological Education, however, the problem of violence among adolescents and young adults in the United States seems inextricably linked to the failure of the nation's educational system to provide first-class basic schooling for many children. Put summarily, there is a parallel between a health system that excludes 37 million citizens from basic care and a system of local schools that labels as basic education what is all too often a gateway to a lifetime of inequality in the workplace and in society.[11] Recently, a group of 12 educators and distinguished citizens, sponsored by the Institute for Philosophical Research, presented *The Paideia Proposal* to address the need for reform of basic education, so as to achieve the goal of universal schooling of uniform quality for all children in the United States.[12]

Many of the problems identified by the Paideia group are similar to those identified by university faculties concerned with the tendency of schools of higher education (including medical schools) to emphasize highly specialized vocational knowledge, rather than the general knowledge needed by all students. *Paideia* is the Greek word (whose root is familiar in pediatrics) for the general, unspecialized learning that every child should experience, equivalent to the more familiar Latin word *humanitas*. The Paideia analysis concludes that schooling of equal length (quantity), but unequal content (quality), fails to prepare *all* children for the continuation of general learning in adult life. Moreover, a dichotomous approach to basic education is identified as a major factor contributing to a climate of disillusionment, rejection, alienation, and resentment among those children and young adults (and their families) who are denied the opportunity to travel first class in school.

By tracking some pupils along an academic, precollege path, and others along a specialized vocational path, society explicitly persists in the conviction of an earlier era that only some students are educable, and sets in place a caste system among its children. The Paideia manifesto holds that all students should receive the same quality and quantity (12 years) of basic schooling, since they all have the same three objectives in life: to take advantage of every future opportunity society offers for self-improvement; to be adequately prepared for discharging the duties and responsibilities of citizenship; and to obtain the basic skills that are necessary to earn a living in our society, no matter what specific job or career they subsequently pursue.

It is of special interest and importance for neurologists among the full-time and voluntary faculties of our nation's medical schools that the Paideia proposal also calls attention to the limitations of didactic instruction, although this format of passive learning is certainly necessary for the acquisition of organized knowledge in many fields of basic learning. There is again a parallel between the Paideia preference for the development of intellectual skills and an enlarged understanding of major ideas and issues by means of problem solving, coaching exercises, supervised practice, and particularly seminars, when these formats are compared with the renewed emphasis on problem-based learning in medical education and other fields of higher learning.[13]

CONCLUSIONS

An overview of the changing burden of illness among the industrialized Western democracies during the 20th century and the rapidly rising costs of more effective medical care suggest that each nation must target for action its priority health problems, determined by means of a population perspective. With this approach, violence is identified as a major health problem in the United States, where it is often associated with substance abuse and the culture of poverty, especially among minority children and young adults. Although medical care, social services, the judicial system, and other sectors of society can make distinct and important contributions to society's collective effort to ameliorate the enigma of violence, educational measures are likely to be the most effective (and cost-effective) steps over the longer term. This judgment arises in part from the growing awareness among many people that we have an undemocratic process of basic education in our nation's schools that must be reformed. Instead of responding to the same objectives that all children seek in their basic education by providing a uniform course of study for all, many schools support instead a program consisting of two or more tracks, only one of which goes straight ahead. The consequences of this separate and unequal approach include a process of disaffection and alienation among many children and young adults, not only toward this kind of schooling, but also toward the society that provides it.

Recently, the Paideia group of educators and concerned citizens has responded to these concerns by developing a proposal for reform of basic education in the United States. The assumption of this group is that we cannot achieve true social justice without schooling that is of uniform quantity and quality among children in all socioeconomic groups of society. All children must receive 12 years of the same course as a generic preparation for work, citizenship, and life. Didactic lectures should be supplemented with problem-solving exercises to develop intellectual skills, and especially with seminars that augment students' understanding of the essential and indispensable ideals and values of our society as reflected in our shared literary and artistic heritage. Neurologists and other physicians can respond to the enigma of violence by supporting essential reform of education in the communities where they have established medical practices.

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Violence

The Neurologic Contribution: An Overview

Frank A. Elliott, MD

• **The role of cultural forces in either promoting or discouraging interpersonal violence is so obvious that it has been allowed to obscure the part played by biologic disorders in determining responses to endogenous and environmental challenges. Neuroscientists and clinicians have demonstrated, however, that aggression has a neuroanatomic and chemical basis, that developmental and acquired brain disorders contribute to recurrent interpersonal violence, that both biologic and sociologic factors are involved, and that to ignore either is to invite error.**

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The term *violence* will be used in this article to indicate physical interpersonal aggression with the intent to harm or destroy. The article is not concerned with collective aggression or with the violent responses of psychotic patients to delusions, illusions, and hallucinations, or with a single episode in a normally well-controlled subject, or with the opportunistic or premeditated predatory aggression carried out for profit in street violence and in drug-related activities. Rather, it focuses on a relatively small percentage of the population who have been given to recurrent violence since childhood or early adolescence—what Hamparin et al[1] called "the violent few." Thus, in a study of 627 chronic offender delinquents from a cohort of 10 000 male individuals born in 1945, 6% were responsible for 71% of the homicides, 73% of the rapes, and 69% of the aggravated assaults.[2]

Since Kaplan[3] reported that trauma to the brain can lead to recurrent violent behavior in previously equable individuals, this has been found to occur following other disorders, including tumor, encephalitis, stroke, multiple sclerosis, Alzheimer's disease and other dementias, cysticercosis, cardiorespiratory arrest, Huntington's chorea, severe hypoglycemia, and other metabolic disorders.[4] However, such brain insults do not add greatly to the total sum of human destructiveness, and their importance lies in the fact that they demonstrate that the response of the brain to environmental or endogenous challenges can be profoundly altered by quite small lesions at specific sites, *whatever the nature of the lesion.*

A much rarer event is the abolition of a lifelong tendency to explosive behavior as a result of brain damage. A woman with a pineal tumor reported as a first symptom the loss of a lifelong tendency to explosive behavior. The tumor was found to have infiltrated the midbrain at the level of the inferior colliculus and the rostral aspect of the cerebellum.[5] A 60-year-old man who had suffered from episodic dyscontrol since adolescence had several transient ischemic attacks, which aggravated his aggressive behavior. Then, following another attack, his personality changed abruptly. He became gentle and had no further rages until his death a year later. An examination of his brain revealed multiple bilateral infarcts, but there was nothing to indicate which was responsible for his pacification (unpublished case).

THE NEURAL SUBSTRATE OF AGGRESSION AND VIOLENCE

Experimental work in animals and clinical studies in man have shown that the capacity for aggression, and for its control, is vested in a system of neuronal assemblies, both excitatory and inhibitory, which are situated bilaterally in the orbitofrontal cortex, the septal area, hippocampus, amygdala, head of caudate nucleus, thalamus, ventromedial and posterior hypothalamic nuclei, midbrain tegmentum, pons,[6,7] and in the fastigial nuclei and anterior lobe of the cerebellum. Under normal conditions, the neocortex also exerts some degree of control over this equipment, but its inhibitory capacity is fragile and can break down in the face of overwhelming endogenous drives or exogenous provocation in normal individuals. Focal lesions confined to the cortex (from bullets and shrapnel) are not as a rule followed by aggressive behavior.

The elicitation of violence by electrical stimulation at various points within the brain sheds much light on the anatomic substrate of violence and its control. The "centers" at which stimulation can give rise to affective aggression in animals are approximately the same as in man; the trigger areas for predatory aggression are slightly different. However, the results of stimulation can be difficult to interpret, because it is sometimes hard to distinguish between the effects of stimulation at one point

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and the more diffuse excitation of other areas by the after discharge.[8] Again, in animals, the effects of stimulation depend, to some extent, on the presence of an appropriate prey. Care also has to be exercised in extrapolating effects of electrical stimulation from animals to man. It is much more difficult to elicit rage in man than in animals, perhaps because of differences in the mental "set" of an animal incarcerated in an operating chair or cage and a human patient undergoing the procedure in the hope of finding an answer to the burden of recurrent rages or seizures. Second, the animal's brain is presumably normal, whereas in most human patients it is not.

Little is known about the neurologic substrate of predatory aggression in man. The predatory behavior of some survivors from encephalitis, including encephalitis lethargica, with its impulsivity, lack of conscience, and egocentricity, more closely resemble a prefrontal syndrome than anything else; yet, most of the damage is in the midbrain and limbic system.

Suppressor areas for affective aggression include the prefrontal cortex, the septal area, the head of the caudate nucleus, the lateral amygdala, the cortex of the anterior lobe of the cerebellum, and the fastigial nuclei.[9-13]

From published articles[14-19] and personal observations, it seems that when small tumors or cysts have been associated with episodic violence, they have usually been situated in a position to involve the limbic system or its connections, usually in or near the midline, thus involving those portions of the brain that we have inherited from our reptilian and early mammalian ancestors. Apathy, the converse of irritability, is also a notable feature of deep midline tumors and cysts involving the anterior corpus callosum, the septum pellucidum, the cavum Vergae, the cingulate gyri, and the third ventricle.[20]

The cerebellar factor, although comparatively new to clinicians, has interested neuroscientists for some time. We do not ordinarily associate subtentorial lesions with mental and emotional disorders, and when they occur, as they did in 47% of 110 cases of cerebellar and other subtentorial tumors,[21] they are apt to be interpreted as a reaction to fear or incapacity, although this explanation is unacceptable when the mental symptoms are the first to appear and intracranial pressure is normal, or when, as in three personal cases, recurrent rages appeared for the first time after the successful removal of midline cerebellar tumors (an angioma and a grade I glioma) and following a presumed right-sided infarct.

In 1947, Moruzzi[22] reported that in thalamic cats spontaneous outbursts of sham rage were inhibited by weak electrical stimulation of the cerebellar cortex just behind and just in front of the fissura prima, but they were elicited as a rebound response if the stimulus was timed to occur during an interval of quietness. Maiti and Snider[23] reported that stimulation of the cerebellar cortex exerted a tonic inhibitory influence on the amygdala and hippocampus by way of the fastigial nuclei. This inhibitory effect could be abolished by electrocoagulation of the rostral midbrain reticular formation. In the cat, stimulation of the rostral fastigial nuclei elicits hypertension, grooming, feeding, and predatory attack behavior.[24] The results of these early experiments encouraged attempts to control both seizures and extreme violence in man by electrical stimulation of the cerebellum. Heath[25] was able to control violent aggressive behavior in schizophrenics by using a pacemaker to stimulate the anterior lobe of the cerebellum. Cooper[26] used a similar technique for the control of seizures; it also stopped attacks of rage.

Recent research has greatly expanded the conception of cerebellar affects on the forebrain. Clinical studies,[27,28] reinforced by magnetic resonance imaging and positron-emission tomographic scans, have demonstrated that the normal human cerebellum is involved in the learning process, in judging the passage of time, in the cognitive processing of words, and, perhaps, in the learning of motor skills. The effect on motor functions is provocative in that many adults with episodic dyscontrol have a history of difficulty in learning common motor skills and/or a lifelong tendency to clumsiness.

The neurochemical substrates for the instigation and control of violent behavior include excitatory and inhibitory neurotransmitters and a variety of longer lasting humeral neuromodulators, including gonadal hormones.

Although most of the work in this field has been carried out on animals of various species, there is a remarkable concordance between animal studies and human data. In man, both γ-aminobutyric acid and serotonin inhibit both predatory and affective aggression and there is a strong positive correlation between a history of angry aggressive behavior and norepinephrine levels. The antiaggressive action of serotonin is suggested by a close and consistent correlation between aggression and impulsivity and low spinal fluid levels of 5-hydroxyindoleacetic acid,[29,30] and there is a similar correlation between low serotonin level in the serum platelets of children suffering from the aggressive conduct disorder.[31]

The question arises as to whether the episodicity of both affective and predatory aggression is related, inter alia, to the diurnal, circadian, or seasonal fluctuations in the levels of many neurotransmitters and neuromodulators, fluctuations that may help to explain not only the episodicity of violence but also the seasonal fluctuations in the rates of homicide and suicide.[9,10]

THREE TYPES OF VIOLENCE

Episodic Dyscontrol

The term *episodic dyscontrol*, first used for attacks of rage resulting from neurotic conflicts, has been applied to a wider range of individuals in whom it appeared for the first time as a result of a brain insult or in whom it has been present from childhood or early adolescence in association with other developmental defects. It corresponds to the intermittent explosive disorder of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (*DSM-III*) and to the episodic violence of Pincus and Lewis,[32,] and it is important for its social impact as one of the causes of unpremeditated homicide, suicide, senseless attacks on strangers, spouse battery, child abuse, criminally aggressive driving, wanton destruction of property, and savage attacks on animals.[33] It occurs both in heterosexual and in homosexual partners of either sex.

Episodic violence cuts across many diagnostic boundaries, but it occurs in only a minority of cases in each disease category. It occurs in psychoses, neuroses, borderline disorders, conduct disorders in children, psychopathy, organic brain syndromes, epilepsy, mental retardation, metabolic diseases, and in developmental syndromes including attention-deficit–hyperactivity disorder (ADHD) and specific learning disorders.

Kaplan, in 1899, described what he called the *explosive diathesis* in these words,

> . . . following the most trivial and impersonal causes there is the effect of rage with its motor accompaniments. They may be the most grotesque gesticulations, excessive movements of the face and a sharp explosiveness of speech; there will be cursing and outbreaks of violence which are often directed towards things; there may or may not be amnesia for these events afterwards. The outburst may terminate in an epileptic fit. There is an excessive reaction with inadequate adaptation to the situation, which is so remote from a well considered and purposeful act that it approaches a pure psychic reflex.[3]

The highly charged affect distinguishes it from the cold and callous predatory aggression of the psychopath and from the habitual aggression practiced as a means of survival in city slums and prisons.[34] Sometimes, particularly in women, the violence is verbal. The language is obscene, profane, and out of character—an elderly (60-year-old) quaker lady interrupted a social occasion by starting to villify her husband for no apparent reason. Her speech was garbled and her lips, flecked with foam, were retracted in a feline snarl. The attacks had occurred at intervals since a severe head injury at the age of 19 years. Such verbal attacks often provoke physical retaliation on the part of the male individual, who finds it easier to hit than to talk.

Physical violence often has a primitive quality, kicking, gouging, scratching, biting, and spitting. Windows are broken, doors smashed, and furniture wrecked. A young woman breaks her (female) partner's arm. The family cat is swung by its tail and smashed against the wall. A man kills another by a single stab wound to the heart and delivers 30 more to the dead body; such overkill is especially apt to occur when the aggressor is under the influence of drugs, alcohol, or extreme hatred. The attacks are usually followed by remorse except in psychopaths or in social circles where abuse of spouse and children is condoned. Individuals subject to these attacks may exhibit disinhibited behavior in other directions such as alcohol and drug abuse, rape, theft, and traffic citations. This is true of both unconvicted domestic batterers[35] and violent delinquents and criminals.[36,37]

Whatever the origin, whether the underlying problem is psychologic or neurologic, episodic dyscontrol can be triggered by small quantities of alcohol, and large amounts can produce pathologic intoxication in which the signs of drunkenness are not present but behavior is bizarre and sometimes violent, and there is complete amnesia for the episode.[38]

The Psychopath (Antisocial Personality Disorder)

Compared with other male criminals, psychopaths commit disproportionate numbers of crimes, and their crimes are also more violent and aggressive than those of other criminals.[39] The condition is marked by a retardation of social and emotional development without significant intellectual impairments, and it was described by Kraepelin[40] in 1915 as "circumscribed infantilism," a view supported by modern developmental psychology.[41] It is said to involve 3% of male and less than 1% of female individuals in the United States (*DSM-III*).

Psychopathic aggression is usually cold and callous, but the psychopaths are also capable of bouts of rage. In both cases, it appears as a disinhibitory response to minor provocation. The full personality profile includes a mask of superficial charm behind which lie inflated ideas of self-worth, a need for stimulation, impulsivity, poor self-control, shallow affect and incapacity for empathy, lack of remorse, manipulative behavior, a parasitic life-style, social irresponsibility, and multiple short-term sexual relationships.[42,43] Marginal cases, who do not display the fully fledged mosaic, present only fragments of the pattern.[44] A particularly malign combination, ie, impulsivity, aggression, lack of empathy, and lack of foresight, is not uncommon after head injury and encephalitis, and it occurs in a subset of the minimal brain dysfunction complex. It is found at all social levels, from the highest to the lowest, and in gifted individuals as well as in the mildly retarded.

A neuropathologic substrate is indicated by abnormal responses to neuropsychologic tests designed to detect "organicity," nonspecific electroencephalographic (EEG) abnormalities in the majority of aggressive cases, resistance to aversive conditioning, low levels of serotonin metabolites in the spinal fluid of adult psychopaths,[29,30] and a low level of serotonin in the platelets of children with aggressive conduct disorder.[31] Minor neurologic abnormalities are often present. In a study of 93 violent criminals, whose collective profile was that of the psychopath, 40% had EEG and/or neurologic abnormalities, including incoordination, dyspraxias, congenital stigmata, hyperactivity, hyperacousis, and photophobia.[45]

Compulsive Violence

Compulsive violence is rare in patients with the obsessive compulsive disorder. Indeed, Freud taught that such patients *never* carry out their fantasies. However, this is misleading, because it does not apply when compulsive symptoms appear following a brain insult. The epidemic of encephalitis lethargica in 1915 through 1925 produced many such cases in children and adolescents, and other types of encephalitis can also do so. In a personal case, following an attack of encephalitis associated with mumps, a previously normal 10-year-old boy showed a gross change of personality but without impairment of intelligence. He was subject to episodic attacks of rage on minimum provocation and was given to compulsive letter writing. In addition, he had an irresistible compulsion to fondle the breasts of girls and women seen in the street and to force his way into their homes where he indulged himself at knife point. As a result of this, he spent much of his time in prison.

Among my patients with cases of episodic dyscontrol, 21 exhibited concomitant compulsive features. In 18 patients, there was evidence of a neurologic disorder, ie, minimal brain dysfunction (n = 8), temporal lobe epilepsy (n = 4), severe head injury (n = 4), and encephalitis (n = 2). Denckla[46] found neurologic abnormalities in 45 of 54 children with the obsession-compulsion disorder and correlations between obsessive compulsive disorder and ADHD, the choreiform syndrome, and Tourette's syndrome. The inability to inhibit obsessions and compulsions at will suggests a failure of inhibitory mechanisms, which is supported in many cases by the favorable response to serotonin uptake blockers.

PHYSIOLOGIC CORRELATES

Age

The peak of physical violence in the home or in the street is in late adolescence and early adult life, but in the fifth decade or later pathologic violence can occur for the first time in a formerly nonaggressive individual as the result of an organic brain insult, intoxication, or a functional psychosis. Some individuals do not acquire the self-control, foresight, judgment, and social conscience that are commonly associated with the normal adult state until their 30s, and aggressive psychopaths can continue to be highly aggressive beyond middle age. It is sometimes forgotten that the cortex of the association areas of the frontal, parietal, and temporal lobes is not mature, in terms of myelination, until the third or fourth decade.[47,48]

Gender and Aggression

There are gender-determined differences between male and female brains in terms of speed of development, histology, cognitive skills (verbal IQ, for instance), and behavior.[49-51] Most normal male individuals, from cradle to grave, are more prone to physical violence than are most female individuals, and the pathologic violence exhibited by individuals in the form of episodic dyscontrol and predatory aggression is far more common in men. The physiologic differences between the two sexes seem to be the result of prenatal differentiation of the hypothalamic preoptic area as a result of the action of androgens. Another gender-related contribution to domestic violence is the premenstrual tension syndrome that, in some individuals, is accompanied by inadequate self-control or actual physical aggression. Over 60% of violent crimes committed by women occur in the premenstrual week.[52,53]

Genetics

The relationship of genetics to criminality, to violence in particular, has been widely discussed.[54,55] In animals, selective breeding to promote aggressiveness has been widely used in the production of bulls for the bullring and pit bulldogs. It has also been induced by selective breeding under laboratory conditions in mice, guinea pigs, rabbits, dogs and dingos.[56] In man, the XYY chromosome anomaly was credited with predisposing to violent criminal behavior, but some have doubts as to its importance. A more important genetic discovery is that a structural abnormality of the fragile X chromosome is often associated with mental impairment, from retardation to a low normal intelligence, learning difficulties, and behavioral problems such as hyperactivity, violent outbursts, and autistic symptoms. Large, low-set ears, large testicles, and other stigmata have also been recorded. About one fifth of the boys and two thirds of the girls who inherit the chromosome appear normal, but they act as carriers and, therefore, may have children or grandchildren with clinical symptoms.

In a study of personality variables in twins reared apart and reared together, Tellegen et al[57] found that both aggressiveness and capacity for control owed more to genetics than to common family or environmental components. Heredity also appears to have a significant role in conditions that contribute to pathologic aggression, notably the episodic dyscontrol syndrome,[58] ADHD,[59] and psychopathy.[54] Sociologic texts often conclude that when violence "runs in the family" it is necessarily something that has been learned from parents or peers. But this cannot be the entire explanation, because, in many cases, only some of the offspring in a violent household are thus affected. The generational transfer hypothesis has been sharply criticized by Stacey and Shupe[60] and others, and cannot explain the many cases of recurrent aggression that have no identifiable social origin.

NEUROPATHOLOGIC CORRELATES

Neurodevelopmental Disorders

The attention-deficit-hyperactivity disorder is a common antecedent of episodic dyscontrol and other forms of antisocial conduct, which may persist into adult life. It is viewed as a developmental condition that is generally chronic in nature, has a strong biologic and hereditary predisposition, and has a significantly negative impact on the academic and social outcomes for many children.[59]

Zametkin et al[61] have found that in adults with residual ADHD, global cerebral glucose metabolism is lower than in normal control subjects and that there was a significant reduction of values at 30 of 60 sites tested in the cerebrum—some of them subcortical.

The multiplicity of affected areas suggests a developmental defect in a diffuse system, for instance, one involving cortical and subcortical inhibitory mechanisms. This could help explain those cases of ADHD in which disinhibitory behavior occurs in behavior other than inattention and hyperactivity, such as acting on impulse without "reflective delay."[45] Disinhibition may appear in the form of substance abuse, traffic violations, theft, and sexual offenses. This is true of many prisoners convicted of violent crimes, whose histories are studded with episodes of impulsive antisocial behavior.[35-37]

The ADHD was originally linked with specific learning disorders and a heterogeneous collection of cognitive, perceptual, motor, and behavioral disorders that constituted the minimal brain dysfunction syndrome,[62,63] which was first identified by Still[64] in 1902, elaborated by others in the 1950s, and is now out of favor. Clements[65] reported that the 10 characteristics most often cited by 100 authors, in order of frequency, were: hyperactivity, perceptual-motor impairments, emotional lability, general coordination deficits, disorders of attention (short attention span, distractability, and perseveration), impulsivity, disorders of memory and thinking, specific learning disorders (reading, writing, arithmetic, spelling), disorders of speech and hearing, and equivocal neurologic signs and EEG irregularities. This complex has been subdivided into the hyperactivity disorder, the attention deficit disorder, specific learning difficulties, and minor motor disabilities that are usually lumped together as "soft signs."[4,59,62-70] However, there is much overlap between these components. Thus, in a study of developmental dyslexia, Critchley[71] found that some presented additional symptoms including disorders of spatial thought and perception, impaired perception of time, mixed cerebral dominance, defects of speech and language, disorders of motility, and poor figure-ground discrimination. Thirty-six percent showed general awkwardness in gesture, gait, and running, all of which are found in profusion in cases of episodic dyscontrol.

Fragments of the syndrome, with or without a proclivity to violence, are encountered in otherwise normal people as well as in some psychopaths, social misfits, intelligent people who have somehow failed to achieve their full potential, and even in individuals of exceptional intellectual or artistic ability.

The clinical identification of some elements of the minimal brain dysfunction syndrome is fraught with difficulties. Adults seldom volunteer accurate information about any delays there may have been in reaching the milestones of their development. Some forget, and others deny. Some who are aware of their problems do not see them as a matter for medical concern, or suppress information about details that are embarrassing to them, such as dyslexia, difficulty in spelling, an inability to catch or hit a ball, or to perform bimanual tasks such as doing up shoelaces or unscrewing the cap off a bottle. Many of these defects are only apparent in real-life situations. In many, there are motor disturbances including dyspraxias and, more often, mild forms of ataxia and clumsiness. Their spontaneous movements may be maladroit, gauche, and lacking in grace.[71] Left-right disorientation, inability to read a map, and mixed cerebral dominance are common. Many are accident prone. All of this can be present against a background of normal or high intelligence.

Multiple defects usually mean multiple sources of chronic stress. Stresses interact with each other and produce more than a simple summation of individual defects, either biologic or environmental,[72] which often lead to chronic irritability or contribute to explosive behavior. In their joint studies of violent delinquents and criminals, Pincus and Lewis[32] found that a paranoid attitude is common. It would seem to be a natural outcome in individuals who have been punished by parents, jeered at by their peers, scolded by their teachers, pursued by truant officers, rejected by members of the opposite sex, and, finally, incarcerated. The converse of these biosocial interactions is seen in the many individuals who had the benefits of a good home, understanding teachers, and good professional guidance, and who, despite their handicaps, made a good adjustment.

Epilepsy and Aggression

The majority of epileptics are not prone to violence or crime, but when we look at people who are subject to recurrent violence, the incidence of epilepsy is greater than in the general population.[32,35,44,73] This applies particularly to temporal lobe epilepsy, but, in addition to the proved cases, some patients report violent interictal episodes, with or without amnesia, that are difficult to identify on clinical grounds unless the evidence of an EEG is positive. The attacks commonly take the form of a brief disturbance in the quality or content of consciousness, with or without amnesia, and can appear without any history of identifiable seizures. To uncover the presence of these attacks is sometimes a formidable task because the violent adolescent's vocabulary is often insufficiently developed to describe their experiences.

Directed violence, with intent to harm or destroy, is a rare epileptic phenomenon; many deny its existence. A more contentious issue is whether an attack of rage associated with partial or complete amnesia can be caused by a focal limbic discharge distinct from epilepsy. Monroe[45] refers to "epileptoid" attacks, and, in the past, others used the term *epileptic equivalents*. There is evidence that epileptic discharges can produce major mood disorders, including rapid cycling depression,[74] and that an attack of rage can end in a convulsion.

Interictal attacks of aggression are not uncommon in temporal lobe epileptics, but the reported prevalence varies with the source of the cases. As is to be expected, it is higher in epileptics who have been committed to institutions, or who have been referred to neurosurgical clinics, than it is in those who have been referred to outpatient clinics. Rodin[75] recorded pathologic aggression in 4.8% of 700 epileptics. Currie et al[76] found it in 7% of 666 cases of temporal lobe epilepsy of mixed origin and type. Bingley,[77] who drew his data from the neurologic and neurosurgical practices of a general hospital in Sweden, found aggressive behavior in 17% of 90 cases. Gastaut et al[78] reported aggression in 50% of their patients with temporal lobe epilepsy. Falconer et al[79] reported interictal aggression in 38% of 50 patients with temporal lobe epilepsy, and a further 15% had a mild, but more persistent, aggressiveness associated with a paranoid outlook.

It seems that there is a relationship between aggressive behavior and temporal lobe epilepsy, but since most temporal lobe epileptics are not violent it is likely, on present evidence, that the seizures and the interictal violence are due to separate processes arising from pathologic lesions in the temporal lobe.[80,81] This is consistent with the experience that in some patients with temporal lobe epilepsy and interictal attacks of episodic dyscontrol, treatment with carbamezepine reduces the seizures, but it may require the addition of propranolol or other medication to the regimen to control the patients' interictal rages.

ENVIRONMENTAL CORRELATES

The current epidemic of both interpersonal and collective violence cannot be due to a sudden proliferation of biologic disorders. It is a result of social conditions and a decline in the power of cultural constraints.

Tidal waves of crime, many decades apart, have been happening in Europe since the 14th century and in America for 200 years[82,83]; the contemporary experience is far from unique. They have occurred during periods of social, economic, and political change, coupled with decline of cultural values. Then, as now, the escalation of violence was accompanied by an erosion of personal integrity, widespread dehumanization, a contempt for life, material greed, corruption in high places, sexual promiscuity, and increased recourse to drugs and alcohol.[84,85]

When what Eibl-Eibesfeldt[86] described as "the cultural corset" is weakened, human behavior tends to regress. The converse is seen in the relative immunity from violence and other disinhibited behaviors enjoyed by communities and nations that have maintained their social, legal, cultural, and moral constraints. The power of these cultural constraints is illustrated by the low rate of interpersonal violence in Japan. In 1980, there was only one murder in Tokyo, and there were only 48 handgun deaths in the whole country.[87] Even mental patients are not immune to the cultural corset. In relatively nonviolent nations, such as Sweden and Britain, violence is far less common in mental hospitals than in American mental institutions.[88]

Under conditions of anomie, aggression proliferates and becomes more savage.[2] Homicides, especially sex-related serial killings, are more often accompanied by mutilation, dismemberment, and cannibalism. Imitation also plays a role in adolescent violence. Thus, in a London borough, there was a small epidemic of attempted and completed adolescent suicide following the exhibition of an educational film that intended to have the opposite effect. Imitation is, of course, a normal feature of youth; but it also occurs as a symptom of prefrontal lesions in adults.[89]

Another aspect of the current epidemic is the emergence of many young people, mainly male, who, although falling short of classical psychopathy, yet exhibit some of its features. They are narcissistic, lacking in altruism and social conscience, impatient, impulsive, and impenitent. They are given to alcohol and drug abuse and to impulsive violence.[90,91] Significantly, during a period of anomie that occurred in Germany after World War I, Reich[92] encountered a similar epidemic in what he described as impulse-driven characters.

In the past, these epidemics have been brought to an end, presumably by the reimposition of the cultural corset and improvement in socioeconomic conditions.

More tangible environmental factors contributing to violence are guns, alcohol, and drugs. With regard to guns, there is little doubt that the rate of death and disablement on the streets and in the home would drop precipitously if effective gun control were introduced. Psychologically and physically, it is much easier to kill with a gun than with a knife, a two-by-four, or by strangulation.

Alcohol, the most used and abused of drugs, once described as "the solvent of the super ego" is a depressant that initially depresses inhibitors and is thus a cause of disinhibited behavior in normal people and, to a greater extent, in individuals with developmental or acquired brain defects. It plays a major role in both street and domestic violence; some women assert that it is only under the influence of alcohol that the aggressor loses control, and, in many violent confrontations, both the aggressor and the victim are under its influence. It is also recognized that the offspring of an alcoholic mother are prone to a variety of defects, including facial deformities, microcephaly, the ADHD syndrome, learning problems, minor motor defects, behavior disorders, or simply a failure to achieve their potential.

The role of street drugs is too immense a subject for this article and for its author, but a comment may be in order with reference to the possible value of marijuana in the treatment of episodic dyscontrol. Patients who have used it unofficially have said that it is much more effective than any of the drugs prescribed by doctors. Its tranquilizing effect is well known in the drug world and was confirmed by a well-documented case of rabies in an individual in whom attacks of dysphagia, terror, and "excitement" were completely brought under control by placing two grains of hashish on the tongue every hour." This was in 1838.[93]

CLINICAL STUDIES

Many studies have addressed the question of what is wrong with "the violent few." The sociologic literature has continued to blame the environment and to ignore biologic factors, whether neurologic, psychiatric, or metabolic. Indeed, Gelles and Strauss[94] listed 15 social theories of violence, none of which include the brain. But as Radzinowicz, doyen of European sociologists, wrote in 1979, after considering the international perspective, "we have no evidence to demonstrate that advances in prosperity, welfare, or education have reduced the incidence of crime or even restrained its rise."[95] However, the hegemony of sociology is being gradually replaced by the view that behavior, including violence, is the result of interactions between biological and environmental variables.[96,97]

This point of view was expressed by Bach-y-Rita et al[35] in 1971 in their landmark report on 130 violent individuals who came to emergency departments in Boston because of fear of going "out of control" and injuring somebody.[35] They presented a consistent picture of homicidal ideation, repeated acts of aggression, impulsivity, multiple traffic citations, and freqent arrests. There was a high incidence of birth injury, mental retardation, periods of unconsciousness, febrile convulsions in infancy, and head injury. Seven of those individuals had a history of temporal lobe epilepsy, and 30 others had had seizurelike episodes of loss of contact with the environment. More than half of the group had a history of hyperactivity or other features of minimal brain dysfunction. Twelve individuals had subnormal IQs, and nine others showed signs of organic impairment on neuropsychologic testing. The EEG was abnormal in 37 of 79 subjects. Their family histories revealed a high incidence of violence and alcoholism, and there was evidence of psychopathology in many. No one was judged to be psychotic.

The authors made two comments that still apply today. First, half of their patients had sought help in the past but they had not received it—they had been rejected by health professionals and by institutions. Second, the authors found themselves as psychiatrists in the invidious position of having to urge on their colleagues a more rigorous neurologic examination in this type of case.

Medical assessment of the delinquent adolescent is seldom well done. Pincus and Lewis[32] examined the pediatric, neurologic, and hospital record data on 20 adolescent boy delinquents and found that "each medical specialty had failed to identify important medical information that might have contributed to difficulties in adaptation," and they also noted that "specialists even failed to obtain data usually considered relevant to their own field of expertise."

Another uncontrolled study was carried out in a psychiatric clinic by Merikangas[98] on 128 violent patients including 16 murderers. Thirty percent were epileptic, 45% had EEG abnormalities, 23% had other neurologic defects, 25% were retarded, and the computed tomographic scan was abnormal in 9% of the patients.

A third uncontrolled study[4] of 286 recurrently violent individuals was unusual in that it involved patients seen in a private neurologic practice who were mainly of middle and upper socioeconomic status; 95% of them were white, and only 10 were incarcerated. The majority were not poor, oppressed, retarded, or uneducated. Thirteen male individuals were responsible for 18 homicides. In 96 cases, recurrent rage was accompanied by additional minor psychopathology (overt psychotics and psychopaths had been excluded from this study). Episodic dyscontrol had developed in 102 formerly stable individuals after a specific brain insult. In some, the lack of control was partial in that the violence was deflected away from its primary object to a surrogate victim—a pet, furniture, windows. There were 119 cases of the minimal brain dysfunction syndrome, 107 cases of seizures, 51 cases of serious head injury, 13 cases of cerebral tumor, 13 cases of encephalitis, 11 cases of stroke, six cases of multiple sclerosis, three cases of Alzheimer's disease, three cases of cardiorespiratory arrest, one case of Huntington's chorea, and one case of proven hypoglycemia. In two of the patients with tumor, the dyscontrol started after a biopsy of the thalamus and the subcallosal cingulate gyrus, respectively. In six others, the dyscontrol commenced some weeks after the successful removal of a benign tumor involving deep midline structures.

Double diagnoses were common (eg, head injury and seizures). Signs of neuropathology were absent in 18 patients, but in nine of them there was a family history of "a terrible temper" involving two or three generations and affecting about half the siblings in each generation. In 139 cases there was a history of violence in one or more members of a dysfunctional family.

The large number of these patients who had had seizures at some time in their lives was within the same range as those reported by Merikangas[98] and Bach-y-Rita et al.[35] Forty patients had complex partial seizures that were linked to the minimal brain dysfunction syndrome (n = 31), to head injury (n = 5), to brain tumor (n = 5), to encephalitis (n = 3) and to multiple sclerosis (a disease in which seizures are normally expected in only 5% to 6%) (n = 5/6). The computed tomographic scan was abnormal or questionable in 41% of 145 patients and EEG was abnormal in 64% of 245 patients, with a preponderance of nonspecific activity.

A high prevalence of neurologic disorders has also been found in controlled studies that were submitted to statistical analysis. Monroe[45] carried out a detailed neurologic, neuropsychologic, psychiatric, and sociologic study on 93 incorrigibly violent psychopathic criminals in a maximum security institution. The personality profile of the group was that of the psychopath. Monroe used a neurologic scale including birth data, head injury, epileptoid mechanisms, brain insults, congenital stigmata (minor physical anomalies), hyperacousis, photophobia, hypersensitivity to touch, motor strength, incoordination, and apraxia. There was a correlation at the .001 level between the neurologic scale and violent behavior, and at the .05 level and beyond with a psychiatric history for anger, violent behavior, overreactivity, emotional behavior, poor judgment, poor effort to improve self-defeating actions, lack of responsibility, grandiose illusions, hyperchondriasis, fugue states, and specific health concerns. There was a close correlation with neurotic or antisocial traits in childhood, and there were poor peer relationships in adolescence.

In another controlled study, Levine et al[99] investigated 53 delinquents aged between 11 and 16.5 years and compared them with an age-matched group from the same region to ascertain factors predisposing to delinquency including violent behavior. The mean age of the patients was 15.1 years. Twenty percent of them had been convicted for violence. The investigation covered socioeconomic deprivation, perinatal health stress, illnesses, chronic behavior disorders, family disruptions, failure in school, and neurodevelopmental difficulties interfering with learning and social adjustment. The authors found aggressive acting-out behavior in 100% of the delinquent group and in 16% of control subjects. The former also showed a high level of domestic stress and medical problems, including recurrent otitis media before the age of 3 years in 17% of the delinquents and in none of the control subjects. There was a history of socially aggressive behavior and of many developmental difficulties in communication, mathematics, and writing. They found motor problems in 8% of the delinquents and in 2% of the control subjects.

Lewis et al[100] compared 31 incarcerated delinquents and 31 nondelinquents. In the former, they found a history of abuse in childhood, exposure to family violence, severe psychiatric symptoms, many cognitive impairments, minor neurologic signs, and psychomotor symptoms, which together predicted group members for nearly 84%. The most significant variable was abuse and family violence. Paranoid ideation, loose and illogical thought processes, and suicide attempts also distinguished the delinquents from the nondelinquents. Documented seizures were present in 17% of subjects, choreiform movements in 55%, inability to skip in 26.9%, psychomotor symptoms in 67.8%, and severe head injury in 64.2% of subjects. Major neurologic impairment did not distinguish between the two groups.

Denno[101,102] conducted a unique study of the records of 987 subjects who were born at the Pennsylvania Hospital between 1959 and 1962. This group was initially part of the National Collaborative Perinatal Project. The subjects were nonwhite and predominantly of low socioeconomic status. The sample (487 male and 500 female individuals) had been followed up at intervals from birth until the age of 22 years. The study involved examination of the mothers as soon as they started attending the prenatal clinic. Their pregnancies were supervised, as were labors and deliveries. Each child was examined immediately after birth and at intervals thereafter. Researchers collected socioeconomic and family data when the mothers registered and at the child's seventh year examination. School data were available, focusing on academic achievement during the ages of 13 to 14 years and evidence of learning and behavioral disability during school attendance. Police records were collected for children aged 7 through 22 years. Much information was gathered from extensive home interviews with parents or caretakers. Each child was interviewed 16 times in all and was given pediatric examinations three times in the first 7 years. They all received selective intelligence tests at 7 years of age and achievement tests at the ages of 13 and 14 years. Serum lead level estimations, performed at the age of 7 years, were found to be high in repeat offenders.

This exercise carries with it the authority of facts recorded at the time, thus avoiding the dubious validity of retrospective questionnaires. Of 987 individuals, 151 became offenders by the age of 18 years and nearly one quarter of these were arrested for violent crimes. Five percent of the male sample were chronic offenders, a figure which jibes with those in the study by Tracy et al[2] on a cohort of 10 000 male individuals born in Philadelphia, Pa, in 1945, and with the results of a second study of 27 160 individuals born in Philadelphia in 1958,[2] approximately half of whom were male. In Denno's study,[101,102] the chronic offenders were responsible for 61% of the violent offenses. The neurologic differences between them and the control subjects included higher figures for neurodevelopmental disorders (incoordination, articulation), head injury, and serum lead levels at 7 years.

Denno concluded that "biological and environmental variables exert strong and independent influences on juvenile crime, which appeared to be directly related to familial instability and, most important, a lack of behavioral control associated with central nervous system disorders."[101]

Finally, in contrast to the above is a 15-year psychiatric study of 233 male and 66 female felons, many of whom were parolees. In addition to detailed psychiatric studies, Guze[103] carried out repeated follow-up interviews with the spouses and first-degree relatives, and the case histories included a comprehensive questionnaire on health matters including some neurologic symptoms. However, there was no neurologic examination, neuropsychologic testing, or special studies. The conclusion was: "sociopathy, alcoholism and drug dependence of the psychiatric disorders are characteristically associated with serious crimes; schizophrenia, primary affective disorders, anxiety neurosis, obsession neurosis, phobic neurosis, and brain syndromes are not."[103] Nevertheless, Guze predicted "in time neurobiology will become more influential because environmental influences can be understood completely only if biological variation is studied simultaneously."[103]

CONCLUSION

Seven of these eight samples show a much higher prevalence of overt and covert neurologic and neurophysiologic abnormalities in recurrently violent individuals than in nonviolent control subjects or in the population at large. While it is understandable that their cognitive and other handicaps might give rise to irrascibility and paranoia, it is unlikely that they could produce the intermittent Jekyl-Hyde transformation of the personality, the immense physical strength, and the primitive, even atavistic, behaviors of the dyscontrol syndrome. The latter more closely resemble sham rage resulting from gross lesions of the limbic system and midbrain in animals and man. Is it possible that a more subtle pathologic process is at work, such as the multiple developmental microdysplasias and microaneurysms that Falconer et al[79] found in the temporal lobes of some violently antisocial epileptics and that Galaburda[104] has reported in developmental learning disorders?

The increasing awareness of the close connections between recurrent interpersonal violence and anatomic, chemical, and neurologic abnormalities calls for more participation by neurologists in the assessment and pharmacologic treatment of these patients. Their intervention is particularly desirable in forensic cases, because, as pointed out by psychobiological criminologist D. H. Fishbein, ". . . The unfortunate reality for those who come into the courts by virtue of their dysfunction, however, is that the underlying causes of their disorder are inaccurately evaluated or simply unattended."[105]

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The Role of a Sleep Disorder Center in Evaluating Sleep Violence

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• To review the state-dependent nature of violence and present a clinically useful classification of sleep violence, this article reviews our experience with sleep-related violence, establishing a differential diagnosis, methods of evaluation, and treatment options. The study occurs in a full-service clinical sleep disorders center evaluating approximately 1000 patients annually with an active participation of 16 physicians representing seven specialties. The patients were self-, physician-, or court/social service-referred for evaluation of violent or injurious behaviors associated with the sleep period. Interventions were dependent on the final diagnosis following clinical and (usually) sleep laboratory evaluation. The main outcome measures were self-reported. During routine clinical evaluations at a multidisciplinary sleep disorder center, it has become apparent that violence is often state-dependent, occurring only during the sleep period, resulting from a number of both neurologic and psychiatric conditions (including malingering and Munchausen syndrome by proxy). In such cases, careful clinical and laboratory evaluation usually results in a specific diagnosis, with effective therapeutic recommendations. Violence may be state-dependent. It is clear that violent behaviors may arise from the sleep period, often without conscious awareness on the part of the subject. This has social, forensic, and clinical implications, and may help contribute to the understanding of violence in general.

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Recent advances in the field of sleep medicine have permitted the identification and characterization of a wide variety of sleep-related disorders that may result in violent or injurious behaviors. The purposes of this article are to: (1) review the state-dependent nature of violence, (2) outline the various sleep-related disorders associated with violence (both cause and effect), (3) emphasize the role of the full-service sleep disorder center in the evaluation and treatment of these disorders, (4) discuss the forensic and social consequences of such behaviors, (5) offer perspectives on the neurobiologic substrates of such behaviors, and (6) underscore the fact that violence may occur in states of being other than wakefulness.

THE STATE-DEPENDENT NATURE OF VIOLENCE

The concept that sleep is simply the passive absence of wakefulness (W) is no longer tenable. Not only is sleep an active, rather than passive, process, it is now clear that sleep constitutes two completely different states: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Therefore, our lives are spent in three entirely different states of being—W, REM sleep, and NREM sleep. Recent studies have indicated that bizarre behavioral syndromes can occur as a result of the incomplete declaration or rapid oscillation of these states.[1] Although many "mixed states" are relatively benign (eg, narcolepsy), others may be associated with violent behaviors.

SLEEP-RELATED DISORDERS ASSOCIATED WITH VIOLENCE

Violent sleep-related behaviors have been recently reviewed in the context of automatized behavior in general.[2] There are well-documented cases of: (1) somnambulistic homicide, attempted homicide, and suicide; (2) murders and other crimes with sleep drunkenness (confusional arousals); and (3) sleep terrors/sleepwalking with potential violence/injury. A wide variety of disorders may result in sleep-related violence. These are best classified under two categories: neurologic and psychiatric, as outlined in the Table.

NEUROLOGIC

Disorders of Arousal

The disorders of arousal comprise a spectrum ranging from confusional arousals (sleep drunkenness) to sleepwalking (SW) to sleep terrors (ST).[3,4] Although there is usually amnesia for the event[5,6] vivid dreamlike mentation may be experienced and reported.[7] Contrary to popular opinion, these disorders may actually begin in adulthood, and are most often not associated with psychopathology.[7,8] The commonly held belief that SW/ST are always benign is erroneous: the accompanying behaviors may be violent, resulting in considerable injury to the individual, others, or damage to the environment.[2,7]

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Sleep-Related Violent Behavior

Neurologic
1. Disorders of arousal
    - Confusional arousals (sleep drunkenness)
    - Sleepwalking/sleep terrors
2. Rapid eye movement sleep disorder
3. Nocturnal seizures

Psychogenic
1. Dissociative disorders (fugues/multiple personality disorder)
2. Malingering
3. Munchausen syndrome by proxy

Febrile illness, alcohol, prior sleep deprivation, and emotional stress may serve to trigger ST/SW in susceptible individuals.[9-11] Medications such as sedative/hypnotics, neuroleptics, minor tranquilizers, stimulants, and antihistamines, often in combination with each other or with alcohol, may also play a role.[12-14]

Confusional arousals (sleep drunkenness) occur during the transition between sleep and wakefulness and represent a disturbance of cognition and attention despite the motor behavior of wakefulness, resulting in complex behavior without conscious awareness.[15-17] These may be potentiated by prior sleep deprivation or the ingestion of alcohol or sedative/hypnotics before sleep onset.[18] These episodes of "automatic behavior" occur in the setting of chronic sleep deprivation or other conditions associated with state admixture (shoplifting has been reported during a period of automatic behavior in a narcoleptic.)[19-21] Patients suffering from obstructive sleep apnea may experience frequent arousals that may serve to trigger arousal-induced precipitous motor activity.[22]

Treatment of simple ST/SW is often not necessary. Reassurance may be sufficient. In cases of potential violence or severe disruption of other household members, effective treatment has been reported with benzodiazepines, tricyclic antidepressants, psychotherapy, progressive relaxation, and hypnosis.[7,23] The avoidance of drugs, alcohol, and sleep deprivation is also important.

REM Sleep Behavior Disorder (RBD)

Rapid eye movement sleep behavior disorder represents an experiment of nature, predicted in 1965 by animal experiments,[24] recently identified in humans.[20,25] Normally, during REM sleep, there is active paralysis of all somatic muscles (sparing the diaphragm and eye movement muscles). In RBD, there is the compromise of REM sleep atonia, which permits the "acting out" of dreams, often with dramatic and violent or injurious behaviors. The oneiric (dream) behavior displayed by these patients is often misdiagnosed as manifestations of a seizure or psychiatric disorder. The RBD is usually idiopathic, but may be associated with underlying neurologic disorders.[26] The overwhelming male predominance (90%) of RBD[27] raises interesting questions relating sex hormones to aggression and violence.[28,29] The violent and injurious nature of RBD behaviors has been extensively reviewed elsewhere.[7,20,25,26] Treatment with clonazepam is highly effective, with sustained response in 90% of patients.[27]

Nocturnal Seizures

The association between seizures and violence has been long debated. It is plain that, on occasion, seizures may be exclusively or predominantly nocturnal, and result i violent or injurious behaviors.[2,7] Of particular note is th frantic and elaborate nocturnal motor activity that ma result from seizures originating in the orbital, mesial, o prefrontal region.[30-35] "Episodic nocturnal wanderings," condition clinically indistinguishable from other forms o sleep-related motor activity such as complex sleepwalking, but that is responsive to anticonvulsant therapy, ha also been described.[36,37] The treatment of nocturnal seizures is similar to that of diurnal seizures.

PSYCHIATRIC

Dissociative Disorders

Waking dissociative states may result in violence, suc as genital self-mutilation.[38] It is now apparent that dissociative disorders may arise predominantly from the slee period.[7,39,40] Virtually all patients with nocturnal dissociative disorders evaluated at our center were victims of repeated physical and/or sexual abuse beginning in childhood. Diurnal diagnoses included psychogenic amnesia multiple personality disorder, and dissociative disorder not otherwise specified.[41] Specialized psychiatric interventions have been developed in treating dissociativ disorders.[42]

Malingering

Although uncommon, malingering must also be considered in cases of apparent sleep-related violence. Ou center has recently seen a young adult man who developed progressively more violent behaviors, apparentl arising from sleep, directed exclusively at his wife. Thi behavior included beating her and chasing her with hammer. Extensive neurologic, psychiatric, and polysomnographic evaluations were unrevealing. It was felt tha this behavior represented malingering.

Munchausen Syndrome by Proxy

In this recently described syndrome, a child is reporte to have apparently serious medical symptoms, which, i fact, are induced by an adult, usually a caregiver, and often a parent. These children may present to a sleep disorders center for evaluation of apnea, seizures, unusua nocturnal spells, or excessive daytime sleepiness. Surreptitious video monitoring in a sleep laboratory during sleep (with the parent present) has provided essentia documentation of the true cause for reported symptoms.[43-45] When the cause of the problem has been identified, child protection agencies should be notified and immediate psychiatric evaluation for the perpetrato should be available.

PERSPECTIVES

The fact that violent or injurious behaviors may arise in the absence of conscious wakefulness raises the crucial question of how such complex behavior can occur. Examination of extensive animal experimental studies provides preliminary answers. The widely held concept that the brain stem and other more "primitive" neural structures primarily participate in elemental/vegetative rather than behavioral activities is inaccurate. There are overwhelming amounts of data documenting that extremely complex emotional and motor behaviors can originate from these more primitive structures—without involvement of "higher" neural structures such as the cortex.[46-52]

Extrapolating from animal data to the human condition, it has been shown that structural lesions at multiple levels of the nervous system may result in wakeful violence.[53] The animal data provide insights to violent behaviors in the disorders of arousal, RBD, and sleep-related seizures: (1) ST/SW: The behavioral similarities between documented ST/SW violence in humans and "sham rage" as seen in the "hypothalamic savage" syndrome are striking.[54] Although it has been assumed that the "sham rage" animal preparations are "awake," there is some suggestion that similar preparations are behaviorally awake, and yet (partially) physiologically asleep, with apparent "hallucinatory" behavior possibly representing REM sleep dreaming occurring during W, dissociated from other REM state markers.[55] (2) RBD: The oneiric behavior demonstrated by cats with bilateral lesions in the vicinity of the locus coeruleus and by humans with spontaneously occurring RBD clearly arises from and continues to occur *during* REM sleep.[24,26,56] (3) Seizures: Seizure activity arising in the limbic system may spread to other more "primitive" structures, with resultant clinical behaviors, without electroencephalographic involvement of the neocortex.[50]

The prosencephalic system may serve to control and elaborate, rather than initiate, behaviors originating from deeper structures.[51] In confusional arousals (sleep drunkenness) in humans that can result in confusion or aggression, there is clear electroencephalographic evidence of rapid oscillations between W and sleep.[16,17] It may be that such behaviors occurring in states other than W are the expression of motor/affective activity generated by lower structures—unmonitored and unmodified by the cortex.

Other, very important factors beyond the scope of this review include: (1) the known effect of genetics on violence and (2) the well-demonstrated effects of environmental and social factors on the structure and function of the nervous system.[57] The plasticity of the nervous system is greater than previously thought.[58,59] These factors are undoubtedly operant in both wakeful and sleep-related violence.

Keeping in mind not only that sleep is a very active process but that the generators or effectors of many components of both REM and NREM sleep reside in the brain stem and other "lower" centers, it is not surprising that, during sleep, prominent motoric and affective behaviors do occur.

CLINICAL AND LABORATORY EVALUATION OF WAKING, SLEEP/VIOLENCE

The history of complex, violent, or potentially injurious motor behavior arising from the sleep period should suggest the possibility of one of the above-mentioned conditions. Our experience with over 150 adult cases of sleep-related injury/violence has repeatedly indicated that clinical differentiation, without PSG study, among RBD, sleep terror/somnambulism, nocturnal seizures, sleep apnea, and sleep-related psychogenic dissociative states may be impossible.[1,2,7] These behaviors may also become manifest during hospitalization, particularly in the intensive care unit setting.[60]

These conditions are diagnosable and most are treatable. Clinical evaluation should include a complete review of sleep/wake complaints from both the victim and the bedpartner (if available). This should be followed by thorough physical, neurologic, and psychiatric examinations. The diagnosis may only be suspected clinically. Extensive polygraphic study employing an extensive scalp electroencephalogram at a paper speed of 15 mm/s, electromyographic monitoring of all four extremities, and continuous audiovisual recording are mandatory for correct diagnosis in cases of sleep-injury/violence.[2,3,7] Clinical and laboratory evaluations are best performed by experienced clinicians. Due to the complex nature of many of these disorders, a multidisciplinary approach is invaluable.

LEGAL EVALUATION OF SLEEP/VIOLENCE

Sleep-related behaviors may lead to accusations of domestic (spouse/child) abuse or other criminal acts. As with automatic behaviors arising from wakefulness, the identification of a specific underlying neurologic or psychiatric sleep/violence condition does not establish causality for any given act. Guidelines for the determination of the putative role of an underlying sleep disorder in a specific violent act have been outlined elsewhere.[2]

SUMMARY AND IMPLICATIONS

It is abundantly clear that violence may occur during any one of the three states of being. That which occurs during REM or NREM sleep may have occurred without conscious awareness and is due to one of a number of completely different disorders. The majority of these conditions are diagnosable and, more importantly, are treatable. The social and legal implications are obvious.

More research, both basic science and clinical, is urgently needed to further identify and elaborate on the components of both waking and sleep-related violence, with particular emphasis on neurobiologic, neuroplastic, genetic, and socioenvironmental factors. The study of violence and aggression will be greatly enhanced by close cooperation among clinicians, basic science researchers, and social scientists.

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Murder, Insanity, and Medical Expert Witnesses

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• Recent advances in the ability to study brain anatomy and function and attempts to link these findings with human behavior have captured the attention of the legal system. This had led to the increasing use of the "neurological defense" to support a plea of not guilty by reason of insanity. This article explores the history of the insanity defense and explores the role of the medical expert witnesses in integrating clinical and laboratory findings, eg, computed tomographic scans, magnetic resonance scans, and single-photon emission computed tomographic scans. Three cases involving murder and brain dysfunction are discussed: the first case involves a subarachnoid hemorrhage resulting in visual perceptual and memory impairment; the second case, a diagnosis of Alzheimer's disease; and the third case, the controverted diagnosis of complex partial seizures in a serial killer.

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For centuries, the courts have relied on the testimony of expert witnesses.[1] The expert witness is an individual, who as a result of training or specialized experience, possesses knowledge that is not available to the court through usual experience. Forensic medicine dates back to early Egyptian times. Physicians in Greece and Rome testified on medicolegal issues. In 1507, the bishop of Bamberg wrote a penal code (*Les Bambergensis*) that called for physicians to testify in cases of violent death. In 1602, Fortunatis Fidelis of Italy, a leader in the development of forensic medicine, published a text on forensic medicine.[2]

While some have suggested that physicians avoid working with the legal system, others have held that the value of the medical expert witness to the legal process justifies continuing the effort to bring medical information to the courts.[3] The medical expert provides an opinion that the court may give greater or lesser weight depending on the expert's training and experience, the nature and extent of the diagnostic process, and the quality of the reasoning used to arrive at clinical conclusions and legally relevant opinions.

The advances in diagnostic procedures to study brain anatomy and function and attempts to link the findings to human behavior have captured the attention of the legal system. An increasing number of defendants are turning to the "neurological defense" to substantiate a plea of not guilty by reason of insanity (*The Wall Street Journal*. March 4, 1992:A1, A6). One of the most public and, at times, dramatic settings for expert witness testimony is at a murder trial where the insanity defense is at issue. In the majority of cases, the medical experts agree on the diagnosis and on whether or not the accused meets the criteria required to be found lacking criminal responsibility. When the experts agree, there is no "battle." Where there is disagreement, the defense attorney tries to prove that the accused lacked criminal responsibility and the prosecution attorney tries to refute that assertion.

The courts understand that physicians use medical diagnosis as an organizing concept for clinical purposes; however, the courts are much more interested in the signs and symptoms of the disorder. The courts use this information to decide if a legal mental disease or defect exists for the purpose of determining criminal responsibility. Judge Bazelon defined a legal mental disease or defect as ". . . any abnormal condition of the mind which substantially affects mental or emotional processes and substantially impairs behavior controls."[4] The purpose of this article is to discuss the development of the modern insanity defense and to explore the role of the medical expert witness when the accused may suffer from neurologic and psychiatric disorders.

HISTORY OF THE INSANITY DEFENSE

A basic tenet of our legal system is that one must be found blameworthy before punishment may be imposed; therefore, the courts distinguish between those who are responsible for their acts and those who are excused of responsibility. A major crime has two elements. First, there must be an *actus reus* (criminal act). The act must be conscious and voluntary; an act that is the result of automatism, somnambulism, or epilepsy is technically not an act. Second, there must be a *mens rea* (criminal intent). The act must be knowingly or purposely committed.

The tests for criminal responsibility gradually evolved. Henry Bracton, in 1268, merged the strict liability of secular law with the moral intent of church law, bringing the intent component (*mens rea*) to the common law.

The English jurist William Lombarde (1536-1601) wrote, "If a madman or natural fool, or a lunatic in the time of his lunacy, or a child that apparently hath no knowledge of good nor evil do kill a man, there is no felonious act . . .

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for they cannot be said to have any understanding will." In 1723, Justice Tracey wrote his criteria of responsibility, the *Wild Beast Test*. "It must be a man that is totally deprived of his understanding and memory, and doth not know what he is doing, no more than an infant, than a brute, or a wild beast—such a one is never the object of punishment."[5]

In 1843, Daniel McNaughton shot and killed Edward Drummond, secretary to the British prime minister, Sir Robert Peel. McNaughton was found not guilty by reason of insanity. In response to the public outcry at the verdict, the 15 judges of the Queen's Bench were convened. The *McNaughton Test*, the *Right and Wrong Test*, emerged.[6] For a finding of insanity, ". . . it must be clearly proved that, at the time of committing the act, the party accused was laboring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing; or if he did know it that he did not know he was doing wrong. . . ."

The nature of the act refers to the physical characteristics of the act, ie, a knife cuts, a gun fires a bullet. The quality of the act refers to the harmfulness of the act, ie, a cut can cause one to bleed to death, a gunshot can kill. These standards have a low threshold, and the issue of criminal responsibility usually turns on whether the individual could distinguish between right and wrong or knew that the particular act was considered wrong by society. Most courts have interpreted "to know" to include both cognitive and affective appreciation of the particular act.

The *McNaughton Test* was quickly and widely adopted in the United States. With some modifications, the McNaughton Test still endures in many jurisdictions. Other jurisdictions have adopted a portion of the *American Law Institute Test*: "A person is not responsible for his criminal conduct if at the time of such conduct, as a result of mental disease or defect he lacks substantial capacity to conform his conduct to the requirements of law." Throughout its history, the insanity defense has been under attack and, in repeated surveys, fewer than 25% of those polled supported the existence of the insanity defense. The American Bar Association, Chicago, Ill, and others have held that the maintenance of the insanity defense is vital to the moral integrity of the law.[3]

CASES INVOLVING MEDICAL EXPERT TESTIMONY

The study of episodic violence has sought to link brain dysfunction with the aggressive behavior. The results of positron emission tomographic scans, computed tomographic scans, magnetic resonance imaging scans, computerized electroencephalograms, and cerebral angiography may provide vivid images that may dazzle the jury. Neuropsychiatric testing may also lead to pages of seemingly "objective" evidence. However, there is substantial controversy whether a test result, eg, a computed tomographic scan, can be linked to a specific behavioral disorder. While medicine energetically moves forward in its effort to understand aggressive behavior, the courts must continue to approach new medical findings cautiously until there is "virtually certain reliability."[7] The court must determine whether the medical findings in a particular case explain and excuse the behavior at issue or whether the medical findings are not linked significantly to the crime. The court will review all the information about the defendant's history, his behavior around the time of the crime, and other relevant facts put before the court by the attorneys. Legal tests of insanity require a clear and direc link between the significant neurologic and/or psychiatric pathologic findings and the illegal act. The link must include a major impairment in the defendant's ability to undertake a conscious, voluntary, or a knowing or purposeful act.

REPORT OF CASES

Case 1.—A 62-year-old, retired father of five, had a history of hypertension and diabetes mellitus. Five years earlier, he had a subarachnoid hemorrhage secondary to an arteriovenous malformation. A computed tomographic scan at the time of the stroke demonstrated blood in the fourth, third, and both lateral ventricles. The ventricles were of normal size, excluding the temporal horns, which were slightly dilated. There was more blood on the left side, especially in the left thalamic region. A cerebroangiogram showed an arteriovenous malformation, fed by both anterior cerebral arteries and the left middle cerebral artery involving the splenum of the corpus callosum of the left thalamus. He regained consciousness after 3 weeks, and, at discharge from the hospital, he had profound memory impairment and confusion.

He returned home, where he showed modest improvement. He had difficulty remembering things, was very concrete, and was very argumentative with his wife. He eventually decided that she was abusing him and trying to hurt him. He purchased a shotgun. A few days later, he went to the church where his wife was attending services to look for her. In the church parking lot, he spotted a woman of similar age and stature who he mistook for his wife. As he approached the woman with his shotgun, she attempted to lock the doors of the car; he shot her through the windshield. He went home and called the police to report he had killed his wife.

Only after his arrest did he learn that he had mistakenly shot another woman. Neuropsychiatric testing demonstrated a marked inability to move flexibly from one idea to another, visual perceptual impairment, and marked verbal and nonverbal memory impairment, both short term and intermediate.

The expert witnesses retained by the prosecution and the defense essentially agreed on their interpretations of clinical findings and the results of the computed tomographic scan and neuropsychiatric testing. He had a subarachnoid bleed that resulted in cognitive and behavioral changes. The court found that he was too impaired to be found fully responsible and convicted of murder but had sufficient capacity to be found responsible for the lesser charge of manslaughter.

Case 2.—A 79-year-old married, retired businessman was charged with murdering his wife. He suffered from chronic obstructive pulmonary disease but was otherwise in good health, until approximately 4 years before his arrest. At that time, his family began to notice that he was increasingly seclusive and suspicious as well as forgetful about collecting moneys owed him and paying his bills. His family felt it was no longer safe for him to drive and took his car keys. He developed episodes of fecal and urinary incontinence. His vision was failing, and he believed that this was proof that he had colon cancer.

Early one morning, while in their kitchen, he stabbed his wife in the chest. She ran out of the house to a neighbor, who called the police. As the police arrived, he went outside to find out what was going on. Following his arrest, he was evaluated and diagnosed as having primary degenerative dementia, Alzheimer's type, with severe impairment of attention/concentration, learning and memory, and abstraction. His intact orientation and language function belied the severity and global nature of his impairment. An electroencephalogram was performed that showed a marked reduction in alpha activity with diffuse slow waves. A computed tomographic scan was within normal limits.

There was agreement that the history, clinical examination, and laboratory tests pointed to a diagnosis of Alzheimer's disease. The expert witnesses then had to apply the data to the legal test for responsibility. While the vague wording of the tests for lack of responsibility require that the expert work with uncertainty, not an unfamiliar position for the clinician when providing an opinion, the wording does provide the court with necessary flexibility to apply the law to the particular facts of the case. The expert witness disagreed as to the extent of his clinical impairments, but there was agreement that he lacked substantial capacity to meet the requirements of the law and should be found not responsible.

CASE 3.—A 44-year-old married individual was charged with the serial killing of 10 women over a period of 2 years. As an adolescent, he had three separate head injuries with periods of unconsciousness. One head injury included a right-sided skull fracture. He had academic and behavioral problems in high school and left before graduating. Soon after he burglarized a store. After serving in the army, he returned home and burglarized a gas station and committed arson. After serving time in prison he was paroled. Less than a year later he was arrested for killing two children. He served 15 years after pleading guilty to manslaughter. Within a year of being placed on parole, the killings began.

All of the women were prostitutes whose bodies were found in deserted settings. Some of the corpses had been mutilated. The patient reported little or no memory of the killings. He described uncontrollable rage. This led to an exploration of his amnesia and the possible role of a neurologic disorder. An electroencephalogram with nasopharyngeal leads was done and reported normal. A computed electroencephalogram was read by one neurologist to show paroxysmal irritative patterns in the bifrontotemporal areas, more on the right side. A computed tomographic scan showed minimal enlargement of his left lateral ventricle. A magnetic resonance scan was noted to show an old healed, right frontal skull fracture and a cystic lesion in the anterior portion of the right temporal lobe. A single-photon emission computed tomographic scan revealed bilateral scarring of the frontal white matter, more prominent on the left side.

One medical expert witness concluded that the patient's history of head injuries, lack of memory, and rage, along with the laboratory findings, indicated that the murders occurred during the automatism of a complex partial seizure.

The other medical expert witness disagreed and diagnosed malingering. In addition to a lack of history of seizures, there was evidence pointing to sexual sadism and necrophilic activity. The patient was apprehended, after months of an intensive police search, when he returned to the body of one of his victims. In addition, he resisted the urge to kill other potential victims because there were other people nearby. The court found him guilty of murder.

COMMENT

Each of the cases involved the use of medical expertise in assessing the behavior of individuals where there was a question of neurologic and psychiatric impairments. In the case of patient 1, who shot a woman he mistook for his wife, the medical expert is asked to provide an opinion, if possible, to the threshold question, "Does patient 1 suffer from a mental disease or defect?" If this patient has a significant mental disease or defect, usually of severity that psychiatrists diagnose as psychosis, the expert witness must relate patient 1's specific signs and symptoms to the specific act in question.

While the signs and symptoms of illness will remain constant for patient 1 throughout the United States, the legal test of responsibility will vary in different jurisdictions.

The medical expert must be aware of the test for criminal responsibility operative in the jurisdiction where the trial is to be held. The medical expert can expect the attorney to provide the relevant statute. The postsubarachnoid hemorrhage status with memory impairments, visual perceptual problems, concrete thinking, and an organic personality disorder in patient 1 set the stage for the second question. Did these impairments rise to a level of significance such that he could not meet the legal standard for responsibility? The expert must consider not only the clinical data but also the accounts of those who knew or saw the accused around the time of the crime. In addition, police reports, witness statements, and any statements made by the accused are important to review. If the accused flees the scene or hides the weapon, this is often seen as evidence that he "knew" what he had done. Patient 1 returned home and called the police to report he had killed his wife.

The medical expert witnesses agreed that patient 1 had had a subarachnoid hemorrhage secondary to an atrioventricular malformation involving the splenium of the corpus callosum in the left thalamus. However, in other cases, there may be disagreement on the interpretation of a computed tomographic scan or of an angiogram. Reasonable, well-trained, experienced physicians may disagree about the interpretation of both clinical and laboratory data. The expert witness essentially agreed on their clinical interpretation of the data and arrived at similar conclusions, ie, his capacity to form the requisite intent was markedly impaired. One expert witness opined, with a reasonable degree of medical certainty, that patient 1 met the criteria to be found not guilty by reason of insanity. The other expert was not as certain about the extent of patient 1's impairment. The information provided by the expert witnesses assisted the court in arriving at its verdict and was also taken into account at the time of sentencing. The court found patient 1 guilty of a lesser charge, manslaughter, and tempered that finding by sentencing him to 3 to 9 years in prison rather than the maximum 8.3 to 25 years because he had a "brain disorder."

In the second case, there was substantial clinical and laboratory data that patient 2 suffered from Alzheimer's disease when he stabbed his wife to death.[8] The obvious nature of his impairment, substantiated by careful study by the expert witnesses, provided the court with sufficient information to make a disposition that was acceptable to all. There was informal agreement between the attorneys and the court that patient 2, if he came to trial, would qualify for the insanity defense. Impairment was profound and unremitting in patient 2, and the court found him incompetent to stand trial. He was sent to a secure geriatric unit for further care and treatment.

In the third case, patient 3 was charged with being a serial killer. Since the medical experts arrived at different conclusions, a battle of the experts followed. These so-called battles rarely occur, both because the insanity defense is rarely used and, when the defense is considered, the medical experts hired by the defense and the prosecution usually find themselves in agreement. Less than 0.1% of felonies are dealt with by an insanity defense. Eighty percent of successful insanity defenses are agreed to by the prosecution. When contested, juries find the defendant not guilty by reason of insanity in less than 5% of cases.

In clinical settings, the physician's opinion is framed in the form of a diagnosis and a plan of action. In the legal setting, the physician's opinion is examined to weigh its credibility; it is the trier of fact, the judge or the jury, to arrive at a verdict and a plan of action. Patient 3 was convincing to one physician while another physician thought he was malingering.

The relationship between epilepsy and violence is of great interest to the courts, especially with the increased use of the diagnosis of epilepsy as a legal defense.[9-11] The jury heard testimony about the medical history of patient 3, the various laboratory tests, and the possible diagnosis of complex partial seizures. Efforts have been made to develop guidelines for assessing the likelihood that a crime was committed during an episode of ictal or postictal confusion.[12] The experts had to discuss complex partial seizure in terms the jury could understand. The jury found the evidence for a finding of a mental disease or defect unconvincing, and patient 3 was found guilty of murder.

These cases provide examples of violent behavior that may have arisen from organic mental disorders, epilepsy, or other neurologic conditions. As an increasing number of defendants and their attorneys explore defenses based on these disorders, medical expert witness will have the opportunity to share with the court new knowledge that links brain structure and function with violent behavior. However, the medical expert witness must use caution when bringing new research findings to courts because of the many "false dawns" that medicine has encountered in the past. Nonetheless, reasoned medical information can help the legal system better understand the defendant's actions and arrive at a just legal outcome. The participation of the medical expert witness is important to the process of bringing medical understanding to the legal system.

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Subacute Idiopathic Demyelinating Polyradiculoneuropathy

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• Seven cases of subacute idiopathic demyelinating polyradiculoneuropathy had a monophasic illness characterized by progressive weakness of all four limbs that evolved during 4 to 8 weeks. Neurophysiological investigations implied demyelination in all seven cases. In two patients, sural nerve biopsy specimens that were taken showed macrophage-associated demyelination. All patients made substantial or complete recoveries with oral prednisolone (four cases) or without treatment (three cases). None of the patients required ventilation or had autonomic complications. These cases provide a link between the acute idiopathic demyelinating form of Guillain-Barré syndrome and chronic idiopathic demyelinating polyradiculoneuropathy.

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Guillain-Barré syndrome (GBS) was arbitrarily defined by an ad hoc committee of the National Institute of Neurological Disorders and Stroke as an acute polyradiculoneuropathy in which symptoms usually reach their worst within 4 weeks.[1] Patients whose progressive phase lasted longer than 4 weeks but less than 8 weeks were regarded as having a variant of GBS according to those diagnostic criteria. Chronic idiopathic demyelinating polyradiculoneuropathy (CIDP) has been regarded as a closely related condition in which the progressive phase lasts months or years and in which a relapsing course is common. Although several large series of patients with CIDP have been published,[2-5] precise diagnostic criteria have only recently been promulgated by a panel of neurologists for the American Academy of Neurology Task Force on Acquired Immunodeficiency Syndrome[6]; these neurologists stipulated the minimum progressive phase as greater than 2 months. In the meantime, one of the authors (R.H.) had proposed a classification into GBS (progressive phase up to 4 weeks), subacute idiopathic demyelinating polyradiculoneuropathy (SIDP) with a progressive phase from 4 to 12 weeks, and CIDP with a progressive phase greater than 12 weeks.[7] This article describes a consecutive series of seven patients with SIDP. This subacute progressive course was associated with the clinical features of a predominantly motor, relatively mild polyradiculoneuropathy without respiratory failure or marked autonomic disturbances. The underlying pathologic features were shown by biopsy specimens in two cases to consist of macrophage-associated demyelination similar to that reported in GBS[8] and CIDP.[2] These cases were reported to the 10th Peripheral Nerve Study Group Meeting, Arden House, New York, NY, in July 1991.

PATIENTS AND METHODS

The records of all patients with a diagnosis of GBS or CIDP who had attended Guy's Hospital, London, United Kingdom, between 1985 and 1990, were reviewed, and patients were included in this series if their illness had been monophasic with a progressive phase that lasted between 4 and 12 weeks. There had to be neurophysiological evidence of slowing of maximum motor conduction velocity, delay of distal motor latency, or delay or absence of F-wave latency, suggesting a demyelinating neuropathy. Cases were excluded that had paraproteinemia, vasculitis, neoplasm, toxin exposure, metabolic cause, or other systemic cause for the neuropathy. Clinical information was collected retrospectively from the observations of one observer (R.H.). Disability was graded according to the scale of Hughes et al[9] in which 2 was equal to able to walk 5 m without aid but not run, 3 was equal to able to walk 5 m with aid, and 4 was equal to bed bound but not needing artificial ventilation. Sensory impairment was graded as follows: 0, normal; 1, numbness or paresthesias without demonstrable sensory deficit on routine clinical testing; 2, hypoesthesia or hypoalgesia to the wrists or ankles; 3, hypoesthesia or hypoalgesia to the elbows or knees; and 4, hypoesthesia or hypoalgesia to the shoulders or groins. Nerve conduction studies were undertaken by one neurophysiologist (P.P.) with the use of standard percutaneous stimulation and surface recording on adequately warmed limbs. Sural nerve biopsy specimens were taken for diagnostic purposes at the level of the lateral malleolus and prepared for light and electron microscopy and morphometry.[10]

RESULTS

Patients

Seven patients who fulfilled the criteria of SIDP were admitted to Guy's Hospital between January 1985 and December 1990. During the same period, 81 patients with GBS and 50 patients with CIDP, including patients with recurrent GBS, were admitted. The patients were all

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Reprints not available.

Table 1.—Clinical Features*

Patient/ Age,y/ Sex	Preceding Type	Event Interval Before Onset, d	Duration of Progression, d	Worst Disability Grade	Worst Sensory Grade	Facial Weakness	Other Cranial Nerves	CSF Days From Onset	CSF Cells/ μL	CSF Protein, g/L	Steroid Therapy†	Time to Recovery, mo	Follow-up, y
1/21/F	URTI	7	32	2	3	0	0	33	0	0.35	0	7	4.0
2/27/F	None	. . .	37	4	2	0	0	14	0	0.68	+	5	0.7
3/44/M	URTI	17	39	3	3	2	0	11	0	1.60	+	2.5	3.0
4/37/M	CMV	. . .	43	4	2	0	0	19	0	1.00	0	<12	3.5
5/19/F	None	. . .	44	4	0	2	3rd	21	0	0.55	+	5‡	0.5
6/25/F	URTI	56	46	3	2	0	0	31	0	1.20	0	6	0.7
7/20/M	None	. . .	56	4	2	0	0	38	4	0.75	+	6	6.0

*CSF indicates cerebrospinal fluid; URTI, upper respiratory tract infection; and CMV, positive cytomegalovirus IgM antibody test without symptomatic infection.

†Zero indicates not given; plus sign, treatment with oral prednisolone.

‡Recovered except for absent tendon reflexes (emigrated 6 months after onset).

young adults (Table 1), and the progressive phase of their illnesses lasted between 32 and 56 days. Three patients had had the symptoms of upper respiratory tract infections between 7 and 56 days before the onset of neuropathic symptoms. The clinical illnesses were relatively mild, and although four patients were so weak that they were unable to walk even with support, none of them required ventilatory support. Although hypertension was detected in patient 3 (and persisted after the neuropathy had recovered), none of the patients had symptomatic autonomic disturbance. The cerebrospinal fluid (CSF) protein concentration was increased in six of seven patients, but the CSF cell count was normal in all of them. Treatment with oral prednisolone (60 mg) was followed by objective increase in strength within a week in all four patients in whom it was given. Virtually complete recovery had occurred within 6 months in all of the patients, including those who had not been treated with steroids.

The clinical features consisted of a predominantly motor polyradiculoneuropathy that affected proximal and distal muscle groups in the upper and lower limbs (Table 1). The facial nerves were affected in two patients, in one of whom there was also bilateral ptosis and impairment of upward gaze of the right eye. No patient required nasogastric feeding or ventilatory support.

CASE 3.—A male truck driver, aged 44 years, was admitted with tingling of the extremities for 11 days and weakness of the right arm and leg. These symptoms had started 17 days after a feverish illness with cough and headache that lasted 3 days. He was still able to walk but had generalized weakness, absent tendon reflexes, and flexor plantar responses. Pinprick, light-touch, and vibration sensations were impaired in a glove-and-stocking distribution up to the elbows and knees. His blood pressure was 210/115 mm Hg. Results of examination were normal in other respects. The CSF protein concentration was 1.60 g/L, and there were no cells. Findings from hematological and biochemical tests were normal, apart from slight elevation of liver enzyme values that returned to normal 2 weeks later. Nerve conduction velocities were at the lower limit of normal, but distal motor latencies were prolonged and F waves were absent in the right median and left tibial nerves. His hypertension was controlled with atenolol. The patient's condition worsened gradually, and he came to need support to walk, until 39 days after the onset, when treatment with prednisolone (60 mg daily) was started. Within 7 days, he had shown marked improvement that continued, so that his condition returned to normal and he stopped taking steroids after a total of 40 days. At a follow-up visit 3 years later, results of examination were normal, but he died of myocardial infarction later that year.

CASE 4.—A male tavern keeper, aged 27 years, was transferred to our hospital with progressive tingling and numbness and, later, weakness of his limbs for 31 days. At admission to his local hospital 7 days earlier, the CSF protein concentration had been increased to more than 1 g/L (the exact concentration was not stated) without any cells. Findings from routine biochemical and hematological tests had been normal, except that some atypical lymphocytes were reported in the blood film. A test for IgM antibodies to cytomegalovirus was positive. He was able to walk only by shuffling with a frame, and he had a flaccid areflexic tetraparesis with impairment of light-touch sensation in the legs up to the knees and on the fingertips. Position sense was impaired at the toes. The distal motor latencies in the right median and left tibial nerves were prolonged, and the tibial nerve F waves were absent. A right sural nerve biopsy specimen showed macrophage-associated demyelination (see below). Weakness increased slightly during the first 12 days after admission, but then, his condition at first stabilized and then underwent a gradual spontaneous recovery. Five months later, his strength was normal, but the tendon reflexes were still absent. There was no relapse during the next 3 years.

Neurophysiological Findings

Representative results from the neurophysiological tests are given in Table 2. In most cases, other nerves were also tested, and the abnormalities are listed in descending order of frequency in Table 3. In each case, the results were interpreted at the time of the examination as consistent with an acquired demyelinating polyradiculoneuropathy.

Nerve Biopsies

The histopathological changes that had occurred within the sural nerve biopsy specimens from cases 2 and 4 were strikingly similar. There was little apparent fiber loss. In

Table 2.—Neurophysiological Features*

				Median Nerve				Tibial Nerve			Radial Nerve		Sural Nerve	
Patient	Day After Onset	Thenar Distal MAP, mV	Thenar Proximal MAP, mV	Distal Motor Latency, ms	Forearm MCV, m/s	F Wave Latency, ms	AH Distal MAP, mV	Distal Motor Latency, ms	Leg MCV, m/s	F Wave Latency, ms	SAP Amplitude, μV	SAP SCV, m/s	SAP Amplitude, μV	SAP SCV, m/s
1	43	1.2	1.1	11.5	46	47	0.4	10.7	37	Absent	9	55	0	Absent
	165	3.7	3.6	6.2	47	34	1.0	9.2	47	60	7	59	0	Absent
2	15	2.2	. . .	11.3	42	. . .	0.6	9.5	30	. . .	11	55	0	Absent
	32	1.5	. . .	9.0	37	. . .	0.1	10.0	. . .	Absent	5	. . .	. . .	. . .
3	19	. . .	. . .	6.0	46	Absent	2.0	6.6	40	Absent	18	50	9	45
4	30	2.7	2.1	7.0	45	34	1.1	9.5	38	Absent	13	55	4	38
5	21	4.0	. . .	7.0	48	Absent	3.0	8.8	32	Absent	20	. . .	2	50
	42	2.0	2.0	11.0	44	. . .	. . .	. . .	. . .	. . .	11	55	. . .	. . .
6	48	10.0	6.4	3.4	35	Absent	6.4	10.0	32	Absent	28	59	9	43
7	72	7.0	6.0	5.4	44	. . .	3.0	7.4	. . .	70	22	57	16	48
	360	8.0	8.0	3.8	51	31	8.0	5.4	47	51	28	61	25	50
Normal	. . .	>4.0	<10% decrement	<4.0	>50	<32	>2.0	<6.0	>40	<59	>20	>50	>10	>40

*MAP indicates muscle action potential; MCV, maximum motor conduction velocity; AH, abductor hallucis; SAP, sensory action potential; and SCV, sensory conduction velocity.

Table 3.—Frequency of Neurophysiological Abnormalities, Including Repeated Investigations*

Criterion	Nerves Positive/ Nerves Tested, No.	% Positive
Absence or delay of F waves	14/16	88
Increase in distal motor latency	18/21	86
Reduced maximum motor conduction velocity	15/19	79
Small or absent SAP	14/20	70
Reduced amplitude of evoked CMAP	12/20	60
Decrement in CMAP amplitude on proximal nerve stimulation	2/7	29
Increase in SAP latency	1/16	16

*SAP indicates sensory action potential; CMAP, compound muscle action potential.

both cases, the myelinated axons exhibited a bimodal distribution (6970/mm^2 in case 2 and 9640/mm^2 in case 4 compared with the normal range of 7800/mm^2 to 10 800/mm^2), and the mean "g" ratio determined for the myelinated fiber population was 0.62 in case 4 (g ratio in control nerve = 0.59). The unmyelinated fibers had a unimodal fiber diameter distribution, and their frequency (42 750/mm^2 in case 2 and 38 790/mm^2 in case 4) was in the normal range (34 000/mm^2 to 51 000/mm^2). Examination of teased fibers and resin sections revealed evidence of active segmental demyelination in 6% of fibers in case 4 and in 1% of fibers in case 2; in both samples, demyelination was frequently paranodal and was always cell associated. Relatively advanced wallerian degeneration (pale-staining bands of Büngner that contained occasional droplets of myelin debris) was seen in 5% of the teased fibers that were obtained from case 2, but it was not seen in any of the fibers that were obtained from case 4. Active demyelination was confirmed in resin sections (Fig 1), and ultrastructurally, macrophage-mediated demyelination was seen occasionally (Figs 2 and 3). There was an accumulation of floccular amorphous material beneath the innermost layer of the perineurium in both nerves, a finding that was consistent with the fact that mild demyelination was still in progress, or with recent inflammation. There was little evidence of endoneurial edema. Macrophages were observed within the endoneurium (sometimes containing debris) and, occasionally, lying inside Schwann cell basal lamina tubes. A few T lymphocytes (UCHT1+) were present in the endoneurium of case 2, but there was none in case 4. Some myeli-

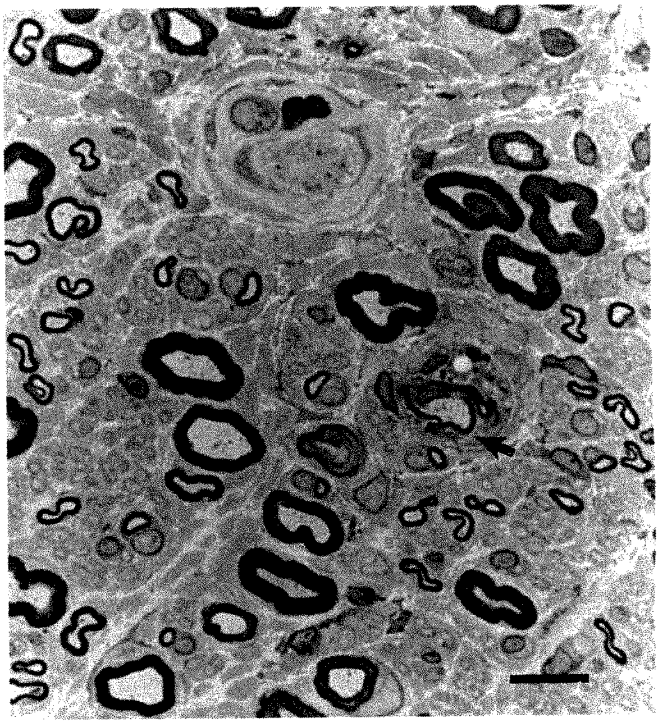

Fig 1.—*Light micrograph shows a myelinated fiber undergoing demyelination associated with an intratubal macrophage that contains myelin debris (arrow). Sural nerve biopsy specimen was obtained from case 4. Bar = 10 μm (thionin and acridine orange).*

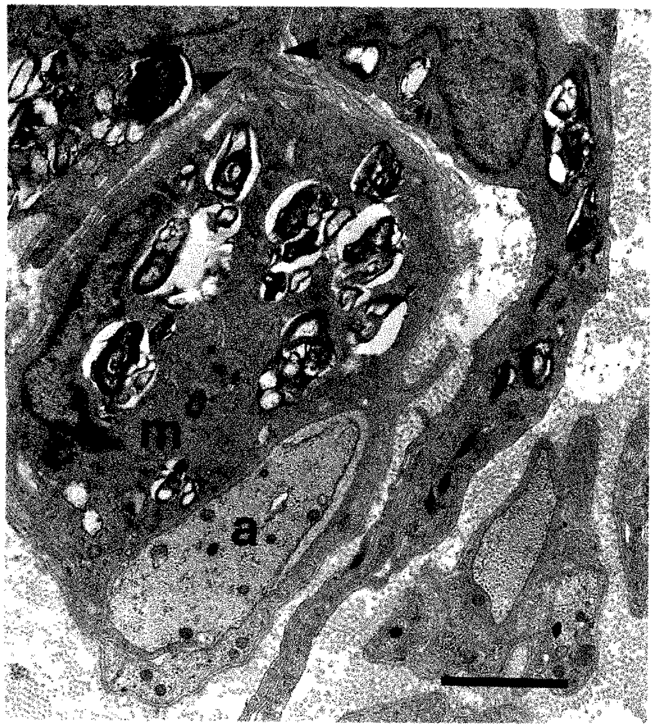

Fig 2.—*Electron micrograph from the sural nerve biopsy specimen that was obtained from case 4 shows a demyelinated axon (a) surrounded by processes of a debris-laden intratubal macrophage (m). The basal lamina has been breached by processes of macrophage cytoplasm (arrows). Bar=2 μm.*

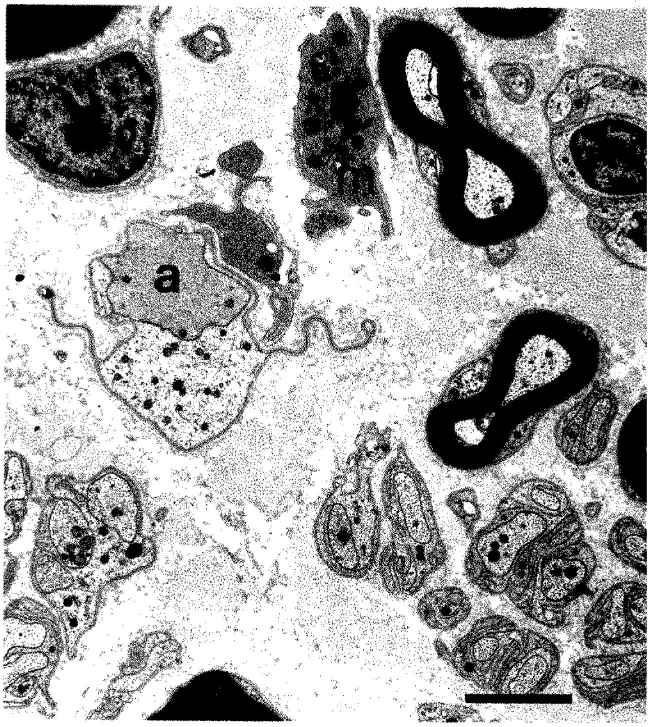

Fig 3.—*Electron micrograph from case 2 shows a demyelinated axon (a) associated with debris-free Schwann cell cytoplasm close to a debris-containing macrophage (m). Bar=5 μm.*

nated axons were surrounded by an inappropriately thin sheath, and some were associated with supernumerary Schwann cells, with both features indicating that these axons had been remyelinated after an earlier episode of demyelination. Five percent of teased fibers, obtained from case 4, exhibited segmental remyelination. Abundant macrophages (MAC387+) were seen in the endoneurium, and small focal perivascular accumulations of T and B lymphocytes (L26+) and macrophages (MAC387$^+$, EBM11+) were seen in the epineurium of both cases. There was no evidence of vasculitis, nor of the presence of amyloid.

COMMENT

In previous publications, patients with what we have called SIDP have been included in series of either GBS or CIDP. Since none of our patients had a progressive phase that lasted between 8 and 12 weeks, we propose in the future to restrict the classification SIDP to this group and to classify patients with a progressive phase of more than 8 weeks (more precise than 2 months) as having CIDP in accordance with the promulgation of the ad hoc committee.[6] The monophasic course with a more or less complete recovery in each case would justify their inclusion as a variant of GBS as proposed in the diagnostic criteria of the National Institute of Neurological Disorders and Stroke committee.[1] On the other hand, the absence of respiratory failure requiring ventilation or serious autonomic complications resembles CIDP more than GBS.[7-11] The clinical features, especially the absence of wasting, proximal as well as distal limb weakness, loss of tendon reflexes, increased CSF protein concentration, and, ultimately, rapid and complete recovery all favor a demyelinating polyradiculoneuropathy as the pathological substrate.

The neurophysiological results support the conclusion that the underlying pathological process was demyelination rather than an axonopathy. In future studies, it might be argued that cases of SIDP should fulfill the rather strict criteria proposed for CIDP by the ad hoc committee[6]; in none of our seven patients was their mandatory minimum of three criteria fulfilled. Three satisfied two criteria, three satisfied only one, and one (case 7) did not satisfy any. However, our data were collected retrospectively from investigations that were obtained in a busy routine clinic to confirm or refute the clinical diagnosis. The tests were undertaken before the criteria of the ad hoc committee had been promulgated; thus, the necessary measurements were often not made. Many results were only borderline as far as the criteria were concerned, but these results were certainly significant in the clinical context. A striking feature of the results is the discrepancy between motor and sensory conduction velocities. Motor slowing was present in at least one segment of the nerve in every patient, except one. By contrast, in only one instance was sensory conduction slowed, and then marginally. The amplitude of sensory nerve action potentials was, by contrast, reduced in the majority. This discrepancy is a feature of all acquired demyelinating polyradiculoneuropathies, whether acute, subacute, or chronic progressive or relapsing, and it is exceptionally rare in other neuropathies. A neuropathy in which at least two nerves show pronounced slowing not due to focal compression, in at least one segment, and in which sensory action potentials are of normal or reduced amplitude but normal latency, turns out in almost every instance to belong to this group. The criteria fail to acknowledge this. To remain content with the criteria as they stand, an indispensable condition of diagnosing CIDP (or SIDP) would lead to the exclusion of undoubted examples of the condition.

Primary demyelination was confirmed as the pathological substrate in the two cases in which nerve biopsy specimens were taken. In both cases, the presence of intratubal debris-laden macrophages suggested that the final common pathway of demyelination was macrophage penetration of the Schwann cell basal lamina and then stripping and digestion of the myelin sheaths. Similar findings have been reported in cases of GBS[8,10,12,13] and of recently relapsed or progressing cases of CIDP.[2,5]

We have not been successful in identifying a serological marker of this relatively mild form of demyelinating polyradiculoneuropathy. The serum from patient 5 contained complement-fixing antibodies to human sciatic nerve homogenate: such antibodies are present in serum from about 10% of patients with GBS.[14] The same serum contained IgM (but not IgG) antibodies to ganglioside GM_1 as detected by enzyme-linked immunosorbent assay.[15] Antibodies to ganglioside GM_1 were present in 15% of 95 patients with GBS, especially in more severe cases with a slow and incomplete recovery, but these antibodies usually belonged to the IgG class.[16] The serum samples from five other patients with SIDP gave negative results with these tests. Serum from patient 6 was not available.

Three of our seven patients had had recognized antecedent upper respiratory tract infections, and one patient without any recognized infection had serological evidence of a recent cytomegalovirus infection. Antecedent infections have been reported before GBS in about 70% of cases[17] and before the onset or relapses of CIDP in about 30% of cases,[18] although the latter figure is uncertain, varying from series to series.[7]

These cases of relatively mild neuropathy with an insidious onset contrast with more rapidly progressive cases that reach their nadir within 4 days and require ventilation.[19] The hyperacute cases usually have electrophysiological evidence of denervation and axonal neuropathy, and recovery is slow and incomplete. Our cases of SIDP can be regarded as occupying a position in a spectrum between GBS on the one hand and CIDP on the other, representing a benign form of both. Although steroid treatment appeared to be beneficial in the four cases in which it was given, the spontaneous improvement in the other three cases raises the question as to whether the former cases would not also have recovered without treatment. Although these cases have had a benign course with no evidence of relapse during an average follow-up of 2.6 years, the possibility cannot be excluded that some of them will relapse in the future and fulfill the criteria for CIDP. Future research should define biological markers of pathogenetic significance that will replace the present arbitrary clinical classifications of GBS, SIDP, and CIDP and provide better guides to treatment.

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Original Contribution

Cerebral Metabolism and Depression in Patients With Complex Partial Seizures

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• Twenty-three patients with complex partial seizures were evaluated with ^{18}F-2-deoxyglucose positron emission tomography and with the Beck Depression Inventory. Five of 10 patients with left and zero of eight with right temporal electroencephalographic foci had depressive symptoms; one of five patients with poorly localized electroencephalographic foci also scored in the depressed range. Temporal, frontal, caudate, and thalamic normalized glucose metabolic rates among five patients with depressive symptoms and well-localized left temporal epileptogenic regions were compared with five patients without depressive symptoms but with similar electroencephalographic characteristics. Multifactorial analysis of variance yielded a significant nonlateralized mood by region interaction. Of nine individual regions compared, only inferior frontal cortex showed a significant difference in normalized regional metabolic rate between depressed and nondepressed patients. Metabolism in this region also distinguished patients with depressive symptoms from normal control subjects. Depressive symptoms in patients with complex partial seizures are associated with a bilateral reduction in inferior frontal glucose metabolism, compared with patients without depressive symptoms and normal control subjects. The frontal lobe hypometabolism observed in patients with depressions associated with epilepsy, Parkinson's disease, and primary affective disorder suggests that similar frontal lobe metabolic disturbances could underlie these conditions.

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Depression is common in patients with complex partial seizures and may be responsible for significant morbidity.[1-7] Positron emission tomography with ^{18}F-2-deoxyglucose (FDG-PET) has been used to study brain metabolism in epilepsy and depression individually; this technique also holds promise for investigating the relationship between these conditions.[8,9]

The most common FDG-PET finding in patients with partial seizures, seen in 60% to 80% of cases, is reduced interictal metabolism ipsilateral to the electroencephalographic (EEG) focus.[10-16] Frequently, the hypometabolic area extends well beyond the identified focus, a phenomenon that may be related to the existence of functional deafferentation, interictal inhibitory activity, postictal metabolic depletion of substrate, or other phenomena.[10,11] The distribution of localized hypometabolism could also be associated with interictal cognitive or behavioral states.

Studies of cerebral glucose metabolism in affective disorders have included patients with unipolar depression, the depressed phase of bipolar illness, depression in the setting of obsessive-compulsive disorder, and depression in Parkinson's disease.[17-23] Frontal hypometabolism, sometimes more marked on the left side, has been observed in several populations.[18-20,22,23] Subcortical differences between depressed and nondepressed subjects have also been reported.[17,19,22] As stated in a recent review,[24] the bulk of the evidence supports decreased inferior frontal metabolism in functional depression.

We undertook this study to further elucidate the metabolic correlates of depressive symptoms and investigate whether previous observations may be extended to patients with partial seizure disorders.

SUBJECTS AND METHODS

Subjects

Twenty-three right-handed patients (10 males and 13 females; mean age, 30.5 years; SD, 7.6; range, 15 to 42 years) referred to the Clinical Epilepsy Section, National Institutes of Health (Bethesda, Md) for uncontrolled seizures served as subjects. Most were studied on the inpatient unit while undergoing evaluation for either surgery or an experimental drug protocol. Hand preference was assessed by the Oldfield Handedness Battery.[25] All patients had complex partial seizures by clinical and EEG criteria,[26] and 18 had secondarily generalized tonic-clonic seizures as well. Using the EEG criteria outlined below, 10 patients had predominantly left temporal, eight right temporal, and five bilateral or indeterminate localization of the epileptogenic region. Informed consent was given by all subjects for neuropsychologic and psychiatric testing and for PET.

Twenty-six control subjects (16 men and 10 women; mean age, 32.8 years; SD, 7.6; range, 21 to 47 years) were evaluated by

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identical FDG-PET techniques, as described below, again after informed consent. Based on history and examination, complete blood cell counts, and biochemistry profiles, these volunteers were free of neurologic, psychiatric, or medical illness and were taking no medications (other than one using oral contraceptives).

Neurologic Evaluation

In addition to detailed histories and physical examinations, all patients underwent computed tomographic and magnetic resonance imaging scanning, routine EEG, and video-EEG telemetry, in 21 cases with sphenoidal electrodes; six patients also had monitoring with bilateral (n = 4) or unilateral (n = 2) subdural electrodes. Determination of seizure focus predominance required concordance among more than 80% of interictal and ictal discharges on scalp recording, or more than 90% of ictal onsets on subdural recording.

Psychiatric Evaluation

Patients were formally interviewed by a psychiatrist (L.A. or T.A.K.) using the Schedule for Affective Disorders and Schizophrenia.[27] The Schedule for Affective Disorders and Schizophrenia is a highly structured, detailed guide in which the interviewer progresses through a series of questions specific to a wide range of diagnoses. Our study focused on those symptoms associated with affective disorders. Patients were assessed for present and past history of affective symptoms.

In addition, all patients completed the Beck Depression Inventory (BDI)[28] to measure the severity of depressive symptoms. The BDI is a 21-item self-rating scale in which each item describes a specific behavioral manifestation of depression. There are four or five self-evaluative statements reflecting a range of severity (0, least severe; 4, most severe) for each item. The scale has been well-validated, and a score greater than 10 is considered to represent depressive symptoms. Scores of 11 to 15 are indicative of mild, 16 to 23 of moderate, and 24 or greater of severe depressive symptoms. Fourteen of the 23 patients were prospectively administered the BDI within 24 hours of their PET scans. Nine patients were given the BDI at more than 24 hours from the time of their PET scan (median, 14 days; range, 1 to 27 days). There was no significant difference between the two groups with high and low BDI scores in interval between BDI testing and PET scanning (median interval for six patients with BDI >10, 4 days; for 17 patients with BDI ≤ 10, 5 days; $P = .47$, Mann-Whitney *U* test).

PET Scanning

All scans were performed on the Neuropet, a seven-slice, four-ring tomograph with in-plane resolution (full-width at half maximum) of 6-mm and slice thickness of 11.5 mm.[29] Three or more scans were consecutively obtained parallel to the canthomeatal line, staggered so that slices were centered 4 mm apart. A calculated attenuation correction was performed on each image, using a program that finds the cranial outline. Adjustment for scattered coincidences was derived from a radioactive phantom with a further software correction for nonuniformity of radioactivity in the patient's head. Scans were carried out 30 minutes after injection of 5 mCi of ^{18}F-2-deoxyglucose. Eyes were patched and ears plugged. A plastic headholder and laser-guided alignment system were used for positioning. Subjects were instructed to remain relaxed but awake, and to avoid concentrating on any one object or mental activity. Electroencephalographic monitoring was performed during all patient scans. Blood samples were obtained from either a radial artery or a hand vein, with heating pads applied to both upper extremities in the latter case (to eliminate asymmetrical sensory input). No patient had a complex partial seizure within 2 hours, or a generalized tonic-clonic seizure within 24 hours, of the FDG-PET uptake period.

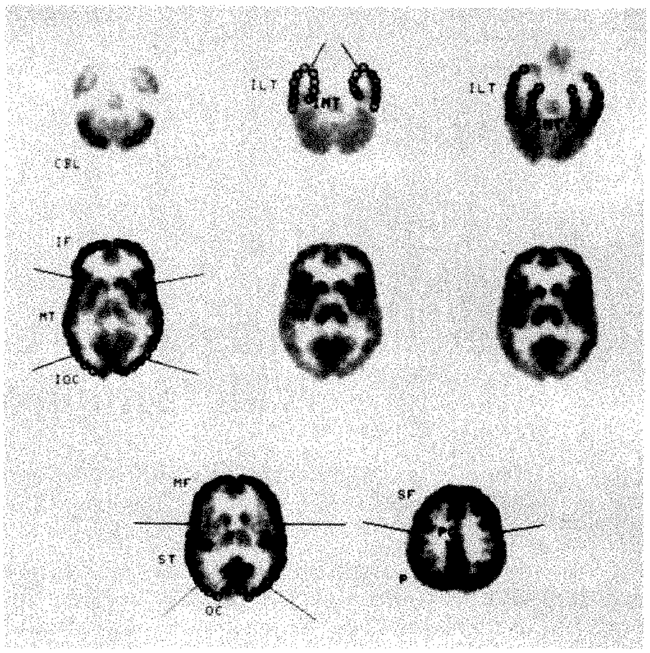

Fig 1.—*Region of interest template for normal control. Fourteen left-sided and 14 right-sided regions are derived from 188 regions of interest as shown. ILT indicates inferior lateral temporal; IMT, inferior mesial temporal; CBL, cerebellum; IF, inferior frontal; MT, midtemporal; IOC, inferior occipital; TH, thalamus; HC, head of caudate; MF, midfrontal; ST, superior temporal; OC, midoccipital; SF, superior frontal; P, parietal; and PC, paracentral.*

PET Analysis

Eight slices were selected for analysis according to criteria established using a standardized tomographic-anatomic atlas.[30] These were selected from the total 21 to 28 slices obtained so as to best match the template. Circular regions of interest 10 mm in diameter were contiguously placed as shown in Fig 1 on gray matter of the cerebellar, lateral, and mesial inferior temporal, thalamic, and caudate regions, and circumferentially around three higher slices, each divided into frontal, temporal, occipital, parietal, and parasagittal areas. Local cerebral metabolic rates for glucose (CMR-glc) were derived for 14 regions on each side by averaging two to 14 regions of interest per region (total of 188 regions of interest). The mean of all 188 regions of interest determined the gray-matter global CMR-glc. Normalized local CMR were obtained by dividing each localized CMR-glc by the global CMR-glc. Normalized local CMR-glc were analyzed as described below for four temporal, three frontal, and two subcortical regions on each side. Analysis was limited to these regions because these are the areas implicated in depression by previous phenomenological[1-9] and functional imaging[17-24] studies, as summarized above and further discussed below; inclusion of all 14 regions would have necessitated still more statistical corrections for multiple hypotheses, decreasing the power of this study to detect intergroup differences suspected on the basis of previous work to be most relevant. Parietal, occipital, and cerebellar regions, therefore, were considered only in the determination of global CMR-glc and were not separately analyzed.

No patient with a right-sided focus scored in the depressed range on the BDI (see the "Results" section). Therefore, to minimize metabolic variability unrelated to mood, primary regional analyses were performed on the depressed and nondepressed subgroups (n = 5 in each group) with comparable left temporal lobe epileptogenic regions.

Statistical Analysis

Multiple-factor analysis of variance examined the effects of region location, region side, and mood (BDI ≤ 10 vs BDI >10) on

Table 1.—Clinical Characteristics*

Patient/ Age, y/ Sex	Cause, If Known	Duration, y	Neurologic Examination	CT/MRI	EEG		BDI Score	Drugs/Levels, mg/L
					Interictal D/C	Ictal Onset		
1/41/F	. . .	38	. . .	nl	L temporal	L temporal	15	Carbamazepine/ 5.0 Valproic acid/30
2/31/M	. . .	28	nl	nl	Bitemporal L>R	Scalp: indeterminate; subdural†: 16/17 L, 1/17 R mesial temporal	14	Carbamazepine/ 10.2
3/33/M	. . .	26	nl	Increased T2 L mesial temporal	L temporal	L temporal	14	Carbamazepine/ 8.4
4/42/M	? Trauma	27	Mild dysnomia	nl	L temporal	L hemisphere	18	Carbamazepine/ 11.5
5/27/F	Hamartoma	6	nl	Calcified lesion L inferior temporal	L anterotemporal	L temporal	11	Carbamazepine/ 8.1 Phenytoin/12.1 Valproic acid/40
6/28/M	. . .	28	nl	nl	L frontotemporal	Scalp: L hemisphere; subdural‡: L mesial temporal	1	Carbamazepine/ 12.4
7/32/F	Meningitis	20	Minimal RHP	nl	L temporal	L hemisphere	0	Carbamazepine/ 13.3
8/32/F	. . .	18	nl	nl	L temporal	L temporal	4	Carbamazepine/ <2
9/27/F	. . .	22	nl	nl	Bitemporal L>R	Scalp: L predominance; subdural†: 6/6 L mesial temporal	8	Carbamazepine/ 11.4
10/32/M	. . .	23	Mild dysphasia	nl	L temporal and diffuse L>R	Scalp: indeterminate; subdural†: L mesial temporal	6	Phenytoin/23.6

*CT indicates computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram; BDI, Beck Depression Inventory; nl, normal; L, left; R, right; D/C, epileptiform discharge; and RHP, right hemiparasis.

†Bilateral subdural electrode implantation.

‡Unilateral subdural electrode implantation.

normalized local CMR-glc among the 10 patients with left temporal lobe epilepsy. Significant regional effects were further analyzed by planned unpaired t tests performed on data for each of the nine regions. Any regions that distinguished depressed from nondepressed patients in these left temporal subgroups were then examined for the entire subject population using t tests to compare depressed and nondepressed patients with each other and with control subjects. A significance criterion of 0.05, modified when indicated by the Bonferroni correction for multiple comparisons, was employed at each stage of analysis. Seizure frequencies before scanning, ages and drug levels among depressed and nondepressed patients were compared using two-tailed t tests, and sex ratios by means of χ^2.

RESULTS

The median score on the BDI was 6. Three men and three women (mean age, 34.5 years; SD, 6.3 years) scored above 10 (median, 14.5; range, 11 to 18), while seven men and 10 women (mean age, 29.1 years; SD, 7.7 years) scored below 10 (median, 3; range, 0 to 9). Age and sex differences between patient groups and between either group and the normal control subjects were not significant. Three (50%) of six patients with high BDI scores and two (12%) of 19 patients with low scores had a history of major depression on the Schedule for Affective Disorders and Schizophrenia. Four (67%) of the six depressed patients and 12 (71%) of the 17 nondepressed patients had generalized as well as complex partial seizures.

Among patients in the depressed range on the BDI, five had a left temporal focus and one had a poorly lateralized, possibly frontal epileptogenic region. Among the nondepressed patients, five had a left temporal focus, eight had a right temporal focus, and in four the focus was bilateral or indeterminate. The difference in BDI classification between left- and right-focus patients was significant by Fisher's Exact Test ($P<.05$). Because of this discrepancy, we decided to perform the primary regional analyses reported below only on patients with left temporal foci, as noted above. Clinical characteristics of these 10 patients are shown in Table 1. Of the five with BDI scores of more than 10, three had BDI within 1 day of their PET scan; of the five with normal BDI scores, four had BDI and PET scans within 1 day of each other (medians of 6 and 5 days,

Table 2.—Normalized LCMR-GLC for Patients With Left Temporal Seizure Foci*

Region	Depressed (N=5) L	Depressed (N=5) R	Nondepressed (N=5) L	Nondepressed (N=5) R
ILT	.76 (.10)	.90 (.05)	.74 (.06)	.93 (.06)
IMT	.70 (.03)	.78 (.02)	.68 (.08)	.77 (.07)
IF	1.04 (.09)	1.02 (.10)	1.15 (.09)	1.18 (.05)
MT	.90 (.09)	.97 (.05)	.92 (.05)	1.06 (.09)
TH	1.08 (.12)	1.13 (.13)	1.09 (.10)	1.12 (.13)
HC	1.16 (.05)	1.20 (.11)	1.21 (.15)	1.20 (.13)
MF	1.11 (.06)	1.09 (.05)	1.10 (.11)	1.16 (.10)
ST	1.02 (.09)	.99 (.07)	1.03 (.09)	1.08 (.04)
SF	1.16 (.09)	1.16 (.09)	1.07 (.02)	1.10 (.09)

*All values are given as means±(SDs). LCMR-GLC indicates local cerebral metabolic rates for glucose; L, left; R, right; ILT, inferior lateral temporal; IMT, inferior mesial temporal; IF, inferior frontal; MT, midtemporal; TH, thalamus; HC, head of caudate; MF, midfrontal; ST, superior temporal; and SF, superior frontal.

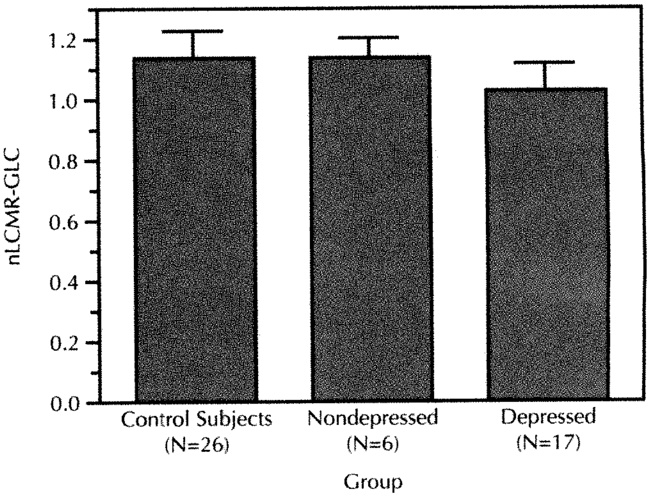

Fig 2.—*Normalized local cerebral metabolic rate for glucose (nLCMR-GLC) in the inferior frontal cortex of depressed and nondepressed patients with complex partial seizures and of normal control subjects. Ratios are given as mean±SD. Depressed patients differ from nondepressed patients and from control subjects; nondepressed patients do not differ from control subjects (see text).*

$P=.5$). Table 2 shows mean normalized local CMR-glc for these patients in each of nine bilateral regions.

Multiple-factor analysis of variance (analyzing region, side, and subject group) on the data summarized in Table 2 yielded highly significant effects for region and side across all 10 subjects ($F=61.8$, $df=8$ for region, $F=15.8$, $df=1$ for side; both $P<.0001$). Side by region interaction was also significant ($F=2.04$, $df=8$, $P=.046$). Individual regional analyses showed that left-sided hypometabolism in the inferior lateral temporal ($F=30.4$, $df=[1,18]$, $P<.0001$), inferior mesial temporal ($F=12.3$, $df=[1,18]$, $P=.0026$), and midtemporal ($F=9.89$, $df=[1,18]$, $P=.0056$) regions accounted for these effects, as might be expected for patients with left temporal epileptic foci. These regional differences remain significant after applying the Bonferroni correction for nine comparisons, yielding an alpha of .006. Mood alone did not significantly affect normalized local CMR-glc for the analyzed regions ($F=3.24$, $df=1$, $P=.074$).

A significant mood by region interaction was observed ($F=2.14$, $df=8$, $P=.036$). Since the mood by region by side interaction was not significant ($F=0.38$, $df=8$, $P=.93$), local CMR-glc for left and right homologous regions were pooled for subsequent planned t tests. These comparisons yielded only one region, inferior frontal, which significantly distinguished the depressed from the nondepressed group ($t=3.65$, $df=18$, $P=.0018$). Since this difference was nonlateralized, all depressed ($n=6$) and nondepressed ($n=19$) patients, regardless of focus localization, were compared with each other and with control subjects ($N=26$) regarding inferior frontal normalized local CMR-glc (Fig 2). Using means of left and right inferior frontal normalized local CMR-glc, patients with BDI scores of more than 10 had significantly less inferior frontal glucose metabolism than patients with lower scores ($t=2.74$, $df=21$, $P=.012$) or control subjects ($t=2.10$, $df=30$, $P=.044$). Nondepressed patients did not differ from control subjects ($t=0.07$, $df=41$, $P=.95$). The two patients with BDI scores in the "moderate" range (≥16) had normalized inferior frontal local CMR-glc of 1.02±.02, while the four patients in the "mild" range averaged 1.04±.04. (No patient had a BDI score in the "severe" range.) Spearman rank order correlation between BDI score and inferior frontal normalized local CMR-glc showed a nonsignificant trend toward an inverse relationship (rho= -.35, $P=.098$). The two patients with the Schedule for Affective Disorders and Schizophrenia interviews suggesting prior depression but BDI scores consistent with a current nondepressed state had inferior frontal normalized local CMR-glc similar to that of the other currently nondepressed patients (1.15±.05).

Seizure frequencies on the day of scanning and over the 6-day period ending with the scan were also examined. For the depressed group, there were a mean of 2.3 seizures (including simple partial seizures) on the day of scanning and 2.8 seizures per day over the 6-day period; for the nondepressed group, corresponding figures were 1.8 and 1.5 ($P>.3$ for both comparisons). Excluding simple partial seizures, the frequencies were 0.5 (day of scan) and 0.6 (6-day period) for the depressed group and 0.9 and 0.5 for the nondepressed group; these differences are also nonsignificant ($P>.6$).

Finally, levels of antiepileptic drugs at the time of scanning were analyzed. Trough levels obtained within 48 hours of PET were available for six of six depressed and 14 of 17 nondepressed patients. Four of the first group were receiving carbamazepine monotherapy, one was receiving carbamazepine and valproic acid, and one was receiving carbamazepine, valproic acid, and phenytoin. In the second group, 10 were taking carbamazepine monotherapy, one was receiving no medication (1 week after being tapered off carbamazepine), three were taking carbamazepine with valproic acid, one was taking phenytoin alone, one was taking phenytoin with valproic acid, and one was taking phenytoin with phenobarbital. Including all patients receiving carbamazepine, levels were 8.8±2.2 and 10.4±2.2 for the high and low BDI groups; this difference was not significant ($t=1.48$, $df=15$, $P=.16$). Numbers of subjects taking the other drugs were too small to assess significance.

COMMENT

This study suggests that (1) patients with left temporal lobe seizure foci are more likely than those with right temporal lobe foci to exhibit depressive symptoms, and (2) the neurophysiologic correlate of these symptoms may be in the inferior frontal rather than temporal lobe, probably bilaterally.

Before further discussion of the implications of these findings, it is appropriate to acknowledge some limitations of the data. First, as mentioned in our previous study,[31] perhaps because of referral characteristics, degree of depressive symptoms among our subjects was only in the mild to moderate range; it is not clear whether results can be extrapolated to severe depression. Second, BDI is a subjective report which, though of demonstrated validity, may underestimate depression in those with less insight or tendency to verbalize symptoms. Third, the variable time interval between questionnaire completion and PET scanning raises the possibility that the emotional state may not have been equivalent on the two occasions. Ideally, patients would complete the BDI immediately before the uptake phase of PET scanning; the correlation in any other situation depends on the time course of variations in both metabolic characteristics of depression and in the BDI score for a given subject. The stability of metabolic correlates of depression is unknown; determination of the relative "state" vs "trait" nature of these characteristics must await longitudinal studies. Regarding the BDI itself, some idea of variability over time in our population may be gained from data gathered for a previous study unrelated to the present article[32]; this included nine patients from the present subject group and 12 additional patients who completed the BDI from two to five times on different occasions ranging from 1 day to several months apart. Only five of these 21 individuals ever "straddled" the cutoff score of 10. We therefore believe that the BDI scores that we used provide a reasonable estimate of our patients' affect at the time of scanning.

The association between left hemisphere lesions and depressive symptoms has been observed previously. Specifically, in relation to epilepsy, many,[7,9,31,33,34] but not all,[35-38] investigators have found this relationship. Some[35,36] have noted a right-sided association, and others[37,38] showed no clear lateralized relationship to mood. In other patient populations, left-hemisphere lesions have been significantly correlated with depressive symptoms.[39-43] Some authors[41-43] in extensive studies with large numbers of stroke patients, consistently found that higher numbers of patients with anterior left hemisphere strokes had concomitant depression compared with those with right-hemisphere or posterior left-hemisphere infarction. Such structural lesions are important in delineating the anatomic structures important in regulating mood states. The functional substrate, however, is not necessarily revealed by anatomic imaging techniques; in stroke, for example, hypometabolism may be observed remote from the infarcted area, presumably reflecting synaptically related areas.[44,45]

In partial epilepsy, hypometabolism is commonly observed to extend beyond the area of structural or EEG abnormality. Even in patients with clear mesial temporal electrical foci, hypometabolism is usually observed in lateral temporal cortex,[16] and often in the thalamus or frontal lobes.[10,12,13] Although in general the clinical correlates of such findings are not well understood, in the case of inferior frontal hypometabolism, our data suggest a possible neuropsychiatric role.

Our finding of frontal hypometabolism in patients with depression and epilepsy is similar to that observed in patients with primary depression and with depression and Parkinson's disease. Furthermore, standard antidepressants appear to be effective in depression associated with primary affective disorders, Parkinson's disease,[46] and epilepsy.[47,48] Although in one study[49] antidepressants were no more effective than placebo in patients with epilepsy, in this study the therapeutic response could have been obscured by an unexpectedly high placebo response rate. The similarity of metabolic abnormalities and of responses to antidepressant drugs in depressions associated with epilepsy, Parkinson's disease, and primary affective disorder suggests that the depression itself may be a correlate, if not a consequence, of frontal hypometabolism independent of the underlying illness.

The frontal lobes are intimately involved in higher integrative functions, such as processing cognitive information; the prefrontal cortex in particular, which includes our inferior frontal region, represents an area of rich anatomic and functional interconnection with many other brain regions, including dorsolateral frontal cortex, amygdala, hypothalamus, septum, medial thalamus, and central midbrain reticular formation.[50,51] The latter may be of particular importance, as suggested by Mayberg et al,[22] who note that the inferior frontal cortex is the main target of the mesolimbic dopaminergic neurons, and the main source of input to midbrain serotonergic neurons of the dorsal raphe nucleus. A deficit in serotonergic transmission has been postulated to underlie both primary depression[52] and depression in Parkinson's disease.[53]

Although patients with depression associated with epilepsy and with primary affective disorders appear to share anatomical and neurochemical characteristics, the mood states themselves may not be entirely equivalent in these two conditions. None of our patients met *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria for depression at the time of their PET scans, mostly because few exhibited neurovegetative symptoms such as change in weight, appetite, sleep, or libido. (Many endorsed a low libido but described this as a chronic problem of at least several years' duration; this may be due to underlying limbic dysfunction or to hormonal or other effects of antiepileptic drugs.[54,55]) These negative findings may also reflect the fact that most of the patients were taking carbamazepine, known to be an effective antidepressant.[56] The BDI is highly weighted toward cognitive aspects of depression, including such categories as sense of failure, self-accusation, and self-hate, and thus may reveal information regarding a certain type of depressive symptoms rather than the syndrome of major depression. Frontal lobe hypometabolism in this context may reflect the effects of cortical rather than subcortical connections, ie, cognitive rather than vegetative manifestations. As such, disturbances of higher cognitive function in other psychiatric disorders such as schizophrenia have been associated with abnormalities in frontal brain regions by PET[23,57-59] and xenon blood flow[60,61] sometimes indistinguishable from those findings in affective disorders.

Limbic system dysfunction cannot at present be thoroughly assessed by PET, since resolution is not fine enough to distinguish small critical limbic structures (eg, hypothalamus or its subnuclei). Consistent findings, in this and other studies, of a relationship between left-hemisphere abnormalities and depression may support hypotheses of lateralized limbic dysfunction either causing depression or providing a physiologic predisposition toward it. Frontal hypometabolism may be related to depressive thoughts and cognitions rather than the full depressive syndrome, representing in essence an epiphenomenon of the mood state. Alternatively, bifrontal dysfunction may constitute a second insult that allows the predisposition toward depression produced by left limbic lesions to become manifest. Mood induction and longitudinal metabolic studies may help clarify these possibilities.

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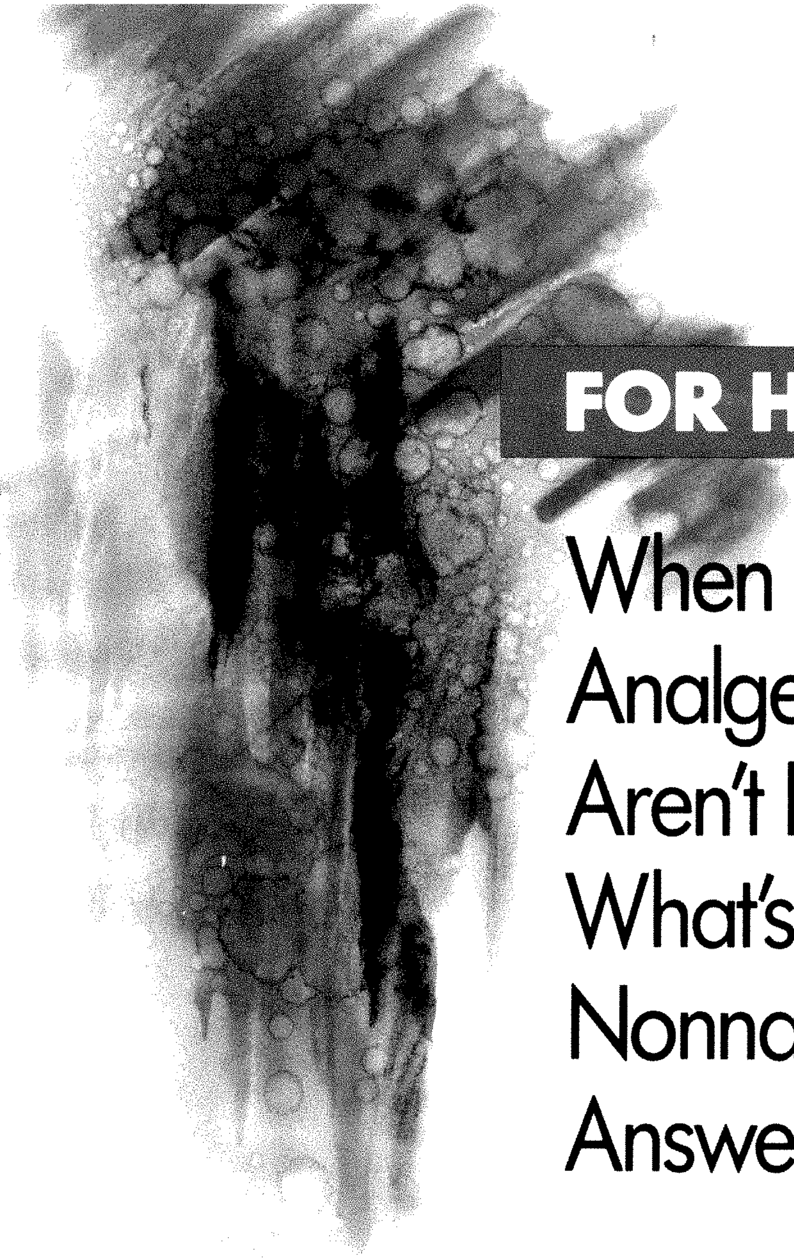

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Acts directly on the serotonin receptors thought to be the source of migraine pain*[1,2]

- FAST RELIEF—In a group of 21 patients treated with D.H.E. 45, the mean pain score dropped 71%† in 30 minutes[3]
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DESCRIPTION

D.H.E. 45® is hydrogenated ergotamine as the mesylate. It is a clear, colorless, stable ampul solution containing per mL:

dihydroergotamine mesylate, USP	1mg
methanesulfonic acid/sodium hydroxide	qs to pH 3.6 ± 0.4
alcohol, USP	6.1% by vol.
glycerin, USP	15% by wt.
water for injection, USP, qs to	1 mL

ACTIONS

Dihydroergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels, and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to ergotamine, the adrenergic blocking actions are more pronounced, the vasoconstrictive actions somewhat less pronounced, and there is reduced incidence and degree of nausea and vomiting.

Onset of action occurs in 15 to 30 minutes following intramuscular administration and persists for 3-4 hours.

Repeated dosage at 1 hour intervals up to 3 hours may be required to obtain maximal effect.

INDICATIONS

As therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so-called "histaminic cephalalgia" when rapid control is desired or when other routes of administration are not feasible.

CONTRAINDICATIONS

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy. Hypersensitivity.

ADVERSE REACTIONS

Numbness and tingling of fingers and toes, muscle pains in the extremities, weakness in the legs, precordial distress and pain, transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged use of dihydroergotamine.

DOSAGE AND ADMINISTRATION

For vascular headache, 1 mL intramuscularly at first warning sign of headache, repeated at 1 hour intervals to a total of 3 mL. Optimal results are obtained by titrating the dose for several headaches to find the minimal effective dose for each patient and this dose should then be employed at onset of subsequent attacks. Where more rapid effect is desired, the intravenous route may be employed to a maximum of 2 mL. Total weekly dosage should not exceed 6 mL.

OVERDOSAGE

Failure to observe the upper limits of repeated parenteral dosage may result in eventual on
of the peripheral toxic signs and symptoms of ergotism. Treatment includes discontinuance of drug, warmth, vasodilators, and good nursing care to prevent tissue damage.

HOW SUPPLIED

As a clear, colorless and stable solution in ampuls containing:

dihydroergotamine mesylate, USP	
methanesulfonic acid/sodium hydroxide	qs to pH 3.6
alcohol, USP	6.1% b
glycerin, USP	15% b
water for injection, USP, qs to	

Ampuls, 1 mL size — boxes of 20.

To assure constant potency, protect the ampuls from light and heat. In the event the ampul sol
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[NOVEMBER 15, 1990 DHE-Z20(BB)]

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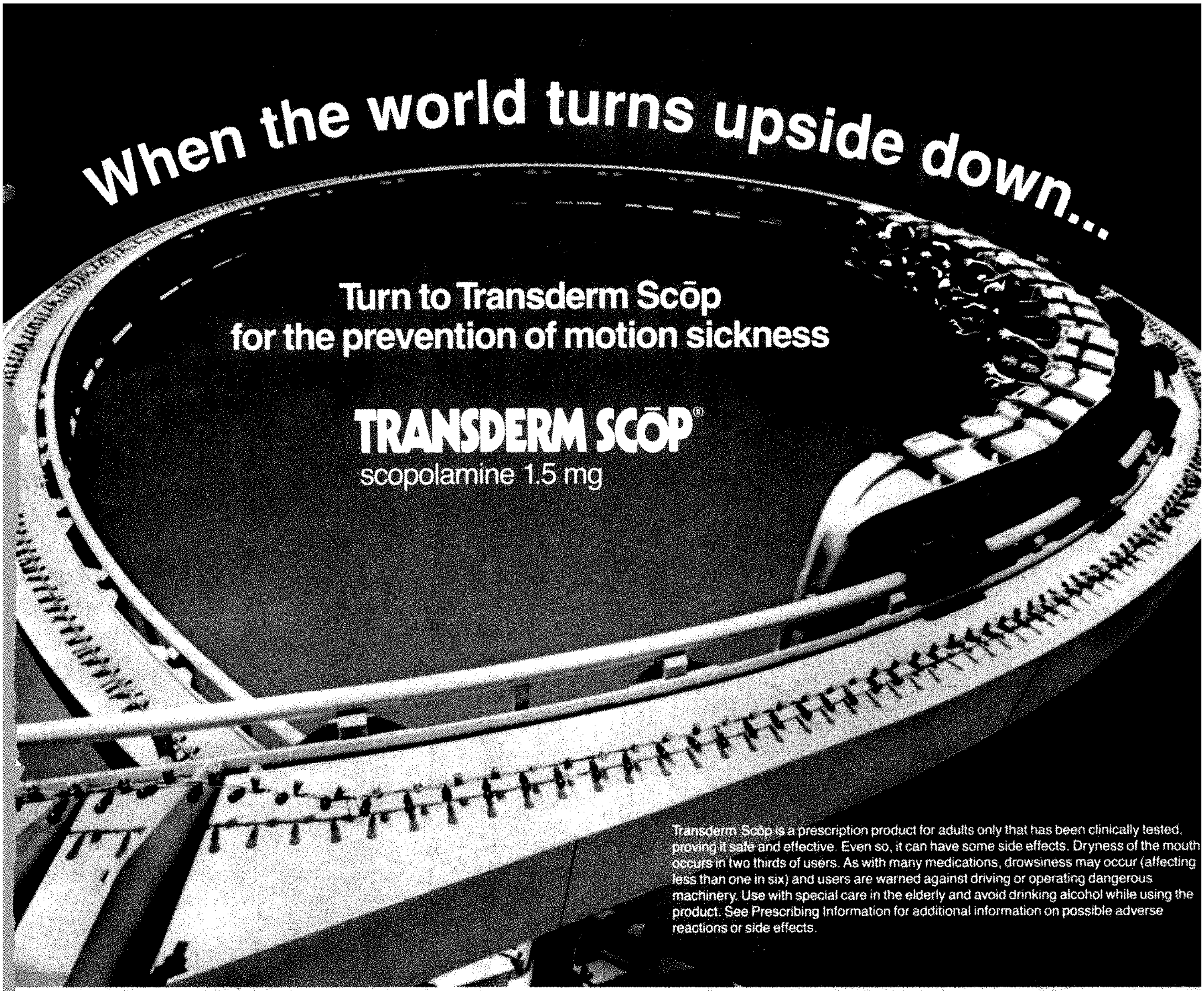
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scopolamine 1.5 mg

Transderm Scōp is a prescription product for adults only that has been clinically tested, proving it safe and effective. Even so, it can have some side effects. Dryness of the mouth occurs in two thirds of users. As with many medications, drowsiness may occur (affecting less than one in six) and users are warned against driving or operating dangerous machinery. Use with special care in the elderly and avoid drinking alcohol while using the product. See Prescribing Information for additional information on possible adverse reactions or side effects.

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scopolamine
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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

Transdermal Therapeutic System

Programmed delivery *in vivo* of 0.5 mg of scopolamine over 3 days

INDICATIONS AND USAGE
Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS
Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS
Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS
General
Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients
Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions
Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C
Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use
Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS
The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE
Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION
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White-Matter Hyperintensity and Neuropsychological Functions in Dementia and Healthy Aging

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• **The relationship between quantitative measurements of brain white-matter hyperintensity (WMH), assessed by magnetic resonance imaging and neuropsychological functions, was explored in demented patients and healthy aged individuals with and without WMH in 12 brain regions. The prevalence of WMH was significantly higher in vascular dementia compared with Alzheimer's disease, especially in posterior periventricular regions. Results showed no difference in any neuropsychological measurement between healthy aged adults with and without WMH. The demented patients with WMH were more impaired in tests of visuoconstruction, attention, finger-motor speed, and latency of tactile identification of objects compared with patients without WMH. These impairments were related mainly to posterior periventricular WMH. There was no relationship between WMH and global cognitive functioning in the demented patients. The degree of WMH was related to age and blood pressure. The data suggest that specific regional WMH may result in specific neuropsychological impairments.**

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Neuropathologically verified white-matter abnormalities have been reported in patients with dementia, as well as in normal aged individuals.[1,2] In vivo, white-matter hyperintensities (WMHs) are demonstrated by computed tomography or magnetic resonance imaging, with the latter technique being more sensitive in detecting WMHs.[3] White-matter hyperintensities are found most frequently in deep cerebral areas, in basal ganglia, and as cappings of the lateral ventricles.[4] White-matter hyperintensities, as identified by magnetic resonance imaging, have been observed both in elderly individuals without neurological deficits[4] and in demented patients.[5] The frequency of WMHs is related to age and blood pressure,[4] but it is still unclear whether WMHs represent a pathognomonic sign for brain disease.

Several hypotheses have been proffered to explain the origin of WMHs. One theory, based on the finding that subcortical hyperintensities have hypertension as a common denominator,[6,7] assumes that arteriolar thickening and sclerosis cause chronic ischemia, perivascular demyelination, and, finally, infarction.[2] Another theory suggests that WMHs represent selective incomplete infarctions without a concomitant complete infarction. This phenomenon is hypothetically related to reduced cerebral perfusion, and it is linked to cardiac output or unfavorable side effects of medical treatment, or other events.[4] A third theory postulates that periventricular WMHs are a result of increased flow of cerebrospinal fluid and a sign of cerebral hydrodynamics that is not necessarily pathological.[8]

Conflicting results have been reported with regard to the effects of WMHs on cognitive functioning. Some studies have failed to find any relationship between WMHs and cognitive performance in nondemented elderly individuals,[9,10] and negative results have also been reported with demented patients.[11-16] Other studies, however, have found that WMHs are related to cognitive deficiencies, both with regard to general effects, such as the degree of dementia,[17,18] and specific effects, such as memory impairment,[19] impairment of verbal abilities,[20] slowness of thought,[19,21] and attentional deficits.[19,20]

There is also research that indicates a relationship between WMHs and affective dysfunction.[20,22-25] Blunted affect has been reported in demented patients with WMHs.[20] Breitner et al[22] presented a case study that lended support to the hypothesis that late-onset psychosis might be related to bilateral WMHs adjacent to the occipital horns of the lateral ventricles, but the generalizability of these data is unknown. Blennow and coworkers[25] reported an association between clinical assessment of confusion and frequency of WMHs in patients with Alzheimer's disease (AD).

The possible cognitive and affective correlates of WMHs have been interpreted as having a subcortical rather than a cortical origin.[20,26] This explanation has been suggested as one reason for failures to demonstrate a relationship between WMHs and cognitive performance, and as a point of consideration in the selection of tests that are sensitive for studying the clinical effects of WMHs. According to Cummings,[27] arousal, vigilance, mood, complex problem solving, and psychomotor speed are neuropsychological functions that are sensitive to subcortical impairment.

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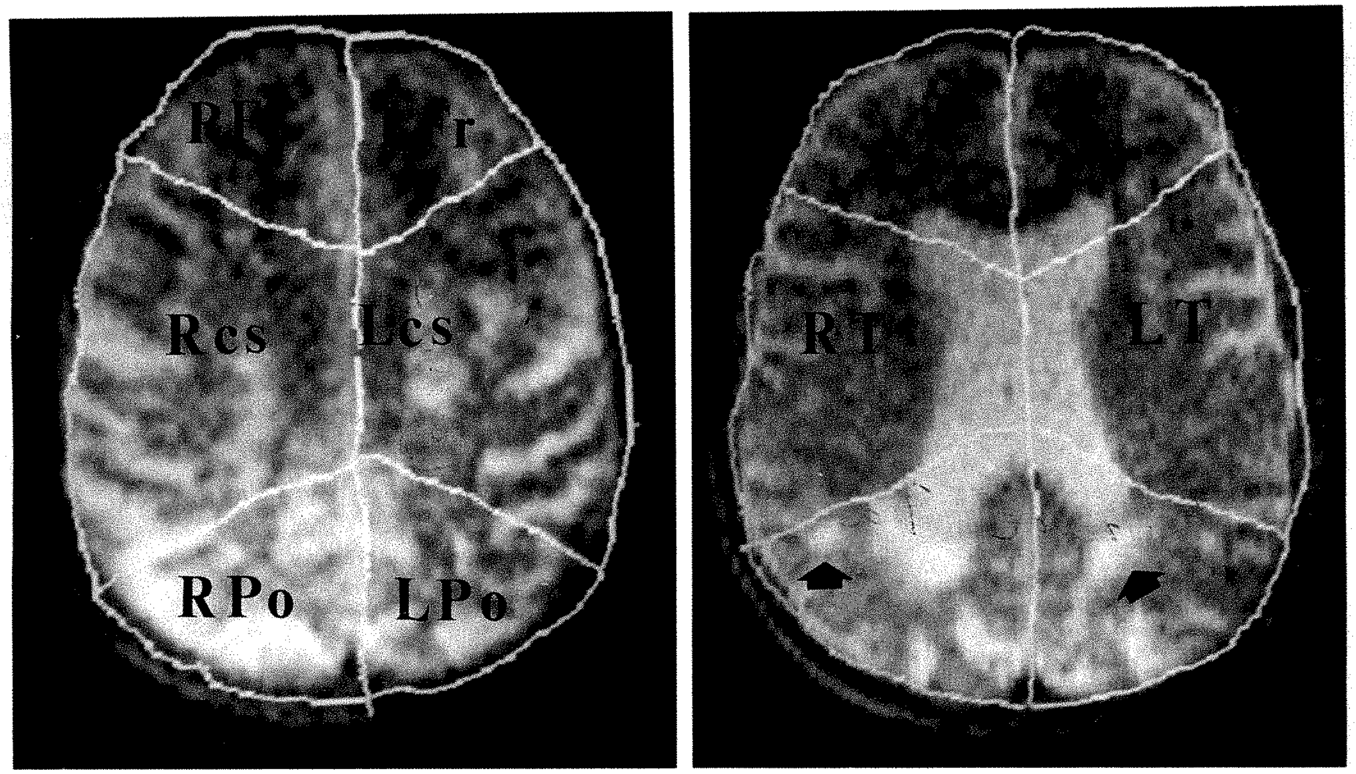

Fig 1.—*Left and right, Regions of interest of white-matter hyperintensities: nonperiventricular left frontal, nonperiventricular right frontal, periventricular left frontal (LFr), periventricular right frontal (RFr), left temporal (LT), right temporal (RT), left centrum semiovale (Lcs), right centrum semiovale (Rcs), nonperiventricular left posterior, nonperiventricular right posterior, periventricular left posterior (LPo), and periventricular right posterior (RPo). Examples of nonperiventricular white-matter hyperintensities are indicated by arrows (right).*

The main purpose of this study was to examine the possible relationships between quantitative regional WMHs and global cognitive performance, as well as specific neuropsychological test results, in healthy aged individuals and demented patients with varying causes of dementia.

PATIENTS AND METHODS

Subjects

One hundred five demented patients participated in the study. They were consecutively referred to the Geropsychiatric Unit at St Göran's Hospital, Stockholm, Sweden, for suspected dementia between October 1, 1987, and December 31, 1989. Twenty-three healthy aged individuals participated in the study as control subjects. They were recruited from a pool of individuals aged older than 75 years who had a "good memory." After examination, according to the same procedure as used for patients (see below), they were found to be healthy,[28] and they could be considered as a group of successfully aged adults.

Procedure

Both patients and control subjects were examined according to the same comprehensive procedure, which included a somatic examination, neurological status, psychiatric status, blood tests (blood hemoglobin, sedimentation rate, erythrocyte indexes [mean corpuscular hemoglobin concentration and mean corpuscular volume], and complete blood cell count), serum tests (glucose, sodium, potassium, calcium, chloride, phosphate, iron, creatinine, albumin, aspartate and alanine aminotransferases, cholesterol, triglyceride, thyroid hormones, vitamin B_{12}, folic acid, human immunodeficiency virus, *Borrelia*, and syphilis), urinalyses (glucose, protein, pH, and microscopical examination), routine electrocardiogram, routine electroencephalogram, chest roentgenography, magnetic resonance imaging (see below), and neuropsychological examination (see below).

Magnetic Resonance Imaging

A low-field magnetic resonance imager that operated at 0.02 T (Acutscan 110, Instrumentarium AB, Helsinki, Finland) gave 12 contiguous transaxial sections through the brain. A highly T_2-weighted pulse sequence (spin echo, 2300/130) was used to get an optimal contrast between WMHs and brain tissue. A mixed T_1- and T_2-weighted pulse sequence (saturated recovery, 500/60 milliseconds) was used to obtain a good separation between cerebrospinal fluid and WMHs.

From the 12 slices, eight were selected for volume measurements, starting with a slice that imaged the optic nerve as the most caudal. The volume estimations were made by one of the authors (G.A.-L.), without knowledge of the clinical status of the subject by using an image processor (GOP-300, Struer-Vision AB, Struer, Denmark). In each slice, the area of increased signal intensity (WMH) was detected and manually outlined with a paint-function (GOP-300, Struer-Vision AB). The area of WMH and the volume of WMH (area of WMH × slice thickness, 10 mm) were calculated. The degree of WMH was expressed as the ratio between the volume of WMH and the intracranial volume from the eight selected slices.

The brain was divided into 12 regions. In Fig 1, the main regions are illustrated. Periventricular WMHs were defined as hyperintensities that were adjacent to the ventricular border, and nonperiventricular WMHs were defined as hyperintensities in the deep white matter that were clearly separated from the ventricles (Fig 1, right, for examples of nonperiventricular WMHs). The examined regions were designated as follows: (1) nonperiventricular left frontal, (2) nonperiventricular right frontal, (3) periventricular left frontal, (4) periventricular right frontal, (5) left temporal, (6) right temporal, (7) left centrum semiovale, (8) right centrum semiovale, (9) nonperiventricular left posterior, (10) nonperiventricular right posterior, (11) periventricular left posterior, and (12) periventricular right posterior.

Table 1.—Age, Sex, and Years of Education for Demented Patients and Healthy Aged Individuals With and Without WMH and for Patients With AD and VD With and Without WMH*

	Demented		Healthy Aged		AD		VD	
	WMH (n=48)	No WMH (n=57)	WMH (n=5)	No WMH (n=18)	WMH (n=15)	No WMH (n=35)	WMH (n=25)	No WMH (n=5)
Mean (±SD) age, y	78.7±5.5	72.3±8.4	78.4±1.9	79.3±2.8	78.9±6.5	72.4±7.7	79.8±4.5	76.2±3.4
Sex (M/F), No.	15/33	21/36	1/4	8/10	4/11	10/25	7/18	2/3
Mean (±SD) education, y	9.8±3.2	10.0±3.8	8.3±1.5	7.0±0	9.1±3.1	10.1±3.8	10.2±3.3	11.5±7.8

*WMH indicates white-matter hyperintensity; AD, Alzheimer's disease; and VD, vascular dementia.

Table 2.—Relative Volume of WMH in Demented Patients and Healthy Aged Adults and in Patients With AD and VD*

	Patients/Adults			Patients		
Region of Interest	Demented (n=105)	Healthy Aged (n=23)	P	AD (n=50)	VD (n=30)	P
Nonperiventricular L frontal	0.006±0.025	0.000	. . .	0.002±0.009	0.016±0.045	<.05
Nonperiventricular R frontal	0.005±0.028	0.000	. . .	0.001±0.008	0.015±0.051	. . .
Periventricular L frontal	0.073±0.156	0.000	<.05	0.036±0.118	0.132±0.190	<.01
Periventricular R frontal	0.084±0.182	0.000	<.05	0.049±0.151	0.138±0.183	<.05
L temporal	0.021±0.099	0.013±0.044	. . .	0.022±0.118	0.030±0.104	. . .
R temporal	0.028±0.120	0.000	. . .	0.029±0.141	0.041±0.127	. . .
L centrum semiovale	0.142±0.393	0.000	. . .	0.103±0.405	0.295±0.464	. . .
R centrum semiovale	0.159±0.402	0.000	. . .	0.100±0.346	0.340±0.520	<.05
Nonperiventricular L posterior	0.000	0.000	. . .	0.000	0.000	. . .
Nonperiventricular R posterior	0.001±0.011	0.000	. . .	0.000	0.003±0.018	. . .
Periventricular L posterior	0.164±0.285	0.021±0.059	<.05	0.070±0.215	0.339±0.317	<.001
Periventricular R posterior	0.184±0.321	0.020±0.056	<.05	0.061±0.185	0.419±0.390	<.001
Total L	0.401±0.797	0.034±0.070	<.05	0.231±0.809	0.805±0.839	<.01
Total R	0.471±0.875	0.020±0.056	<.05	0.239±0.758	1.043±0.993	<.001
Total anterior	0.172±0.345	0.000	. . .	0.088±0.266	0.301±0.368	<.01
Total posterior	0.364±0.615	0.020±0.114	. . .	0.130±0.397	0.722±0.686	<.001
Grand total	0.864±1.649	0.055±0.117	<.05	0.470±1.561	1.779±1.803	<.001

*WMH indicates white-matter hyperintensity; AD, Alzheimer's disease; and VD, vascular dementia. Data are given as mean±SD, except for P values.

Neuropsychological Tests

All subjects were tested by the same experienced neuropsychologist (O.A.) with the Mini-Mental State Examination,[29] six subtests (Information, Digit Span, Similarities, Block Design, Object Assembly, and Digit Symbol) from the Wechsler Adult Intelligence Scales–Revised,[30] two subtests (Associative Learning and Visual Reproduction) from the Wechsler Memory Scale,[31] the Corsi Block Tapping Test[32] (administrated as a span task and according to an up-and-down technique), the Digit Span Test[33] (according to an up-and-down technique), the Simple Reaction Time Test,[34] and the Finger-tapping Test.[34] After April 1 1989, the following tests were added to the test battery: the Boston Naming Test (items 1 through 30),[35] the FAS Word Fluency Test,[36] the Wechsler Intelligence Scale for Children Maze test,[37] a Map Orientation Test (O. M., unpublished data, 1991) the Line Bisection Test,[38] and the Tactile Identification of Objects Test.[39] The six tests from the Wechsler Adult Intelligence Scales–Revised were used to estimate the full-scale IQ.

Diagnosis

One hundred five patients met the criteria for clinical diagnosis of dementia according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.*[40] Fifty patients (47.6%) satisfied the criteria for the clinical diagnosis of AD, as suggested by the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.[41] These criteria are probably the most sophisticated available for the clinical diagnosis of AD. Between 85%[42] and 100%[43] of the cases that satisfy the criteria are later found to have neuropathological changes of AD.

Thirty (28.6%) of the patients met the criteria of vascular dementia (VD) according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*[40]; these criteria included dementia with a history of signs and symptoms that were referable to disturbed cerebral circulation in temporal connection with dementia, and signs of focal disturbances that presented at the neurological examination.

Eight patients (7.6%) had dementia of various specific origins

Table 3.—Neuropsychological Test Results in Raw Scores for Demented Patients and Healthy Aged Adults With and Without WMH and for Patients With AD and VD With and Without WMH*

	Demented		Healthy Aged		AD		VD	
Test	WMH (n=48)	No WMH (n=57)	WMH (n=5)	No WMH (n=18)	WMH (n=15)	No WMH (n=35)	WMH (n=25)	No WMH (n=5)
MMSE	18.0±6.5	17.8±6.4	28.6±1.5	29.1±0.9	17.0±7.2	17.2±6.5	19.0±6.1	18.0±5.6
WAIS-R								
FSIQ	78.5±9.8	78.5±10.1	113.8±3.6	110.7±11.6	78.4±10.4	78.5±11.4	76.6±6.8	76.5±8.8
Information	11.1±6.0	10.9±5.5	21.8±3.3	22.8±4.5	10.2±6.9	11.2±5.6	10.5±4.4	8.4±4.0
Digit Span	9.0±2.8	9.9±3.1	13.0±2.3	13.8±4.2	9.1±2.8	9.1±3.4	8.7±2.8	7.2±1.1
Similarities	8.3±7.1	9.2±6.5	20.2±3.4	21.9±3.2	8.0±7.7	9.5±6.6	7.4±5.5	8.5±7.9
Block Design	4.8±6.0	6.4±6.0	27.8±5.6	21.3±7.7	6.4±7.3	6.8±6.6	4.1±5.4	5.0±4.8
Object Assembly	8.4±6.1	12.4±7.9	27.3±5.7	23.3±6.8	10.3±6.2	12.4±8.6	7.3±5.0	13.8±5.9
Digit Symbol	10.3±7.9	12.3±8.4	47.6±11.2	38.2±11.2	12.0±9.0	13.1±9.4	9.9±6.7	5.5±5.0
Boston Naming	23.5±4.3	25.2±4.0	29.4±0.5	29.3±0.9	21.9±6.0	25.1±4.2	24.3±2.9	26.7±3.1
FAS Fluency	23.8±13.9	27.2±4.0	37.2±5.8	53.4±20.6	30.3±18.2	32.6±18.7	21.6±12.4	. . .
Map test	2.7±2.1	2.6±2.2	0.2±0.4	0.9±0.7	2.3±1.6	2.7±2.2	3.1±2.4	2.0±1.2
WISC								
Mazes	5.0±2.8	4.3±2.6	8.0±0.0	7.7±0.5	7.7±0.6	4.4±2.8	3.9±2.6	. . .
WMS								
Associative Learning	6.2±2.0	6.3±3.3	15.6±2.7	15.3±3.3	5.6±2.0	6.3±3.5	6.5±2.1	5.6±2.4
Visual Reproduction	1.8±1.9	2.5±2.0	8.9±1.5	8.0±2.9	1.4±1.5	2.5±2.3	2.0±2.2	2.1±2.0
Digit Span a m UD	5.1±0.7	5.2±0.8	6.2±1.1	6.3±1.2	4.8±0.7	5.2±0.9	5.2±0.7	5.0±0.2
Corsi Block Tapping								
Span a m UD	3.9±0.8	3.8±0.8	5.5±1.0	5.1±0.5	3.9±0.7	3.8±0.9	3.9±0.8	3.8±0.3
Simple Reaction Time	395±134	340±116	239±11	225±36	393±193	329±117	385±95	407±109
Finger-tapping								
R hand	53.3±10.4	51.0±11.4	54.5±8.9	54.4±6.7	56.4±8.7	53.1±10.0	51.7±11.3	47.4±14.4
L hand	43.9±11.7	45.7±12.4	50.5±6.1	47.9±8.6	48.1±8.8	46.7±9.7	40.0±10.4	49.0±10.0
Alternating hands	50.3±13.0	57.9±12.4	65.3±7.6	54.0±10.3	55.3±11.4	58.4±13.0	45.8±12.0	53.5±16.9
Tactile Identification of Objects								
R hand	3.1±1.5	2.2±0.3	1.6±0.4	0.8±0.9	3.8±0.4	2.3±0.2	2.8±1.8	2.1±0.2
L hand	4.0±2.5	2.2±1.1	1.6±0.3	0.8±0.9	5.7±3.2	2.6±1.1	3.1±1.8	1.8±1.3
Line Bisection								
R eye	−0.2±4.4	1.6±7.9	0.6±2.1	−0.3±1.8	0.8±6.3	−0.8±3.2	−0.8±3.2	16.5±12.0
L eye	0.1±3.8	0.3±2.4	2.0±0.7	−0.5±1.4	0.2±3.0	0.1±2.5	0.0±4.4	3.0±0

*WMH indicates white-matter hyperintensity; AD, Alzheimer's disease; VD, vascular dementia; MMSE, Mini-Mental State Examination; WAIS-R, Wechsler Adult Intelligence Scale–Revised; FSIQ, Full-Scale IQ; FAS, Word Fluency Test; WISC, Wechsler Intelligence Scale for Children; WMS, Wechsler Memory Scale; and a m UD, ad modum up and down (see text for explanation). Data are given as mean±SD throughout.

(Parkinson's disease, alcohol abuse, and brain tumor), and 17 (16.2%) had dementia of unknown origin.

A psychiatric diagnosis was made in six patients, and the conditions of 17 patients were not diagnosed as demented. These 23 subjects were excluded from the study.

RESULTS

The distribution of age, sex, and education in demented patients and healthy aged adults with and without WMHs are presented in Table 1. Table 1 also shows background variables for patients with AD and VD, with and without WMHs. There was a tendency that the healthy aged adults were older than the demented patients (F=3.53, *df*=1/124, *P*=.07), but there was no age difference between the two groups of demented patients. There was no age difference due to the existence of WMHs in the groups of demented patients and the healthy aged adults (F=2.34, *df*=1/124, *P*>.10), although the patients with AD and VD, with WMHs, were older than the patients without WMHs (F=7.47, *df*=1.76, *P*<.01). The sex distribution was not different for demented patients and healthy aged adults with and without WMHs ($\chi^2=1.24$, *df*=1, *P*>.10) or for patients with AD and VD, with and without WMHs ($\chi^2=1.43$, *df*=1, *P*>.10). The demented patients were somewhat more educated than the healthy aged adults (F=5.11, *df*=1/82, *P*<.05), but there was no difference in education between patients with AD and VD.

In the demented patients, the degree of WMHs was related to age (*r*=.24, *df*=103, *P*<.05), systolic blood pressure (*r*=.28, *df*=99, *P*<.01), and diastolic blood pressure (*r*=.24, *df*=98, *P*<.05), but not to blood glucose, triglyceride, or cholesterol. In the healthy aged group, there was no significant correlation between the degree of WMHs and any of these variables.

Table 2 presents the relative volume of WMHs (mean±SD) for demented patients and control subjects. As has been previously reported,[28] we found few observations of WMHs in the control group. Only five (22%) of 23 healthy aged individuals had any WMHs. In the patient group, there were 48 cases with WMHs (46%). The amount of WMHs was significantly larger totally in the demented group compared with that in the control group;

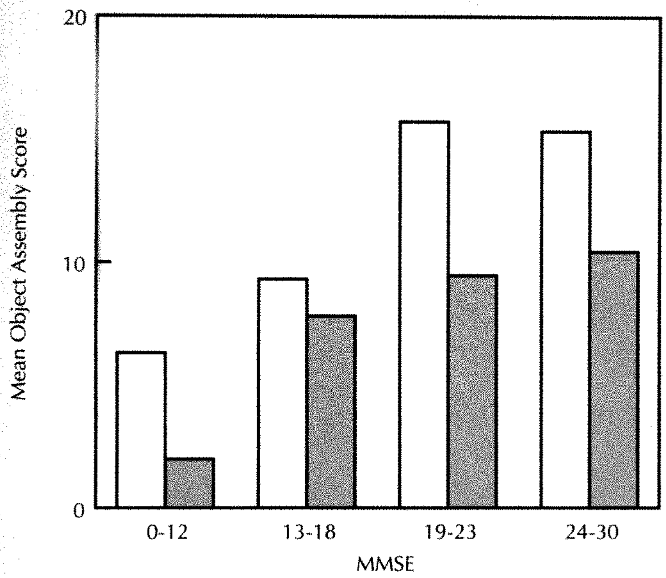

Fig 2.—*Mean score of Wechsler Adult Intelligence Scales–Revised: Object Assembly in demented patients with (shaded bars) and without (open bars) white-matter hyperintensities grouped by severity of cognitive decline according to the Mini-Mental State Examination (MMSE).*

Table 4.—Effect of WMH in Specific Regions on Neuropsychological Performance in Demented Patients*

Region	Neuropsychological Test	P
Nonperiventricular L frontal	None	. . .
Nonperiventricular R frontal	None	. . .
Periventricular L frontal	Simple Reaction Time	<.05
Periventricular R frontal	WAIS-R: Block Design Simple Reaction Time	<.05 <.05
L temporal	None	. . .
R temporal	None	. . .
L centrum semiovale	None	. . .
R centrum semiovale	None	. . .
Nonperiventricular L posterior	None	. . .
Nonperiventricular R posterior	None	. . .
Periventricular L posterior	WAIS-R: Object Assembly Simple Reaction Time Finger-tapping: alternating hands	<.05 <.05 <.01
Periventricular R posterior	WAIS-R: Object Assembly Finger-tapping: alternating hands	<.05 <.05
Grand total	WAIS-R: Object Assembly Simple Reaction Time Finger-tapping: alternating hands Tactile Identification of Objects	<.05 <.05 <.05 <.05

*WMH indicates white-matter hyperintensity; WAIS-R, Wechsler Adult Intelligence Scales–Revised.

the most pronounced difference was in the periventricular regions. In other regions, there were small differences between groups in the amount of WMHs. In the demented group, there were more WMHs in the right than in the left hemisphere ($t=2.76$, $df=96$, $P<.01$). A corresponding effect was not seen in the control group. The amount of WMHs was significantly larger in the posterior than in the anterior regions in both demented patients ($t=3.90$, $df=104$, $P<.001$) and healthy aged individuals ($t=1.76$, $df=22$, $P<.05$).

Table 2 also presents the relative volume of WMHs (mean±SD) for patients with AD and VD in the 12 regions of interest. There were five cases (13%) with WMHs among the patients with AD and 25 cases (63%) among the patients with VD. The total amount of WMHs was larger in patients with VD compared with patients with AD ($t=3.42$, $df=78$, $P<.001$), and especally in the left ($t=4.49$, $df=77$, $P<.0001$) and right ($t=5.57$, $df=78$, $P<.0001$) periventricular posterior regions.

The neuropsychological test results for demented patients and healthy aged adults with and without WMHs are presented in Table 3. Each neuropsychological test was analyzed separately with a group (demented, healthy) × WMHs (no, yes) analysis of variance. As expected, there was a main effect of group in all cognitive tests ($P<.001$), but not in the sensory-motor tests: Finger-tapping, Tactile Identification of Objects, and Line Bisection ($P>.10$). There was no main effect of WMHs for any of the tests. However, according to t tests within the group of demented patients, those with WMHs were more impaired than those without WMHs in the following tests: Object Assembly ($t=2.11$, $df=82$, $P<.05$); Simple Reaction Time ($t=1.81$, $df=88$, $P<.05$); Finger-tapping (alternating hands) ($t=2.48$, $df=68$, $P<.01$); and Tactile Identification of Objects (left hand) ($t=2.19$, $df=18$, $P<.05$). In the group of healthy aged adults, there were no significant differences between those with and without WMHs in any test. For one of the tests that indicated an effect of WMHs in the demented group (Object Assembly), the relative impairment due to WMHs is illustrated in Fig 2, in which the demented patients have been stratified in four groups on the basis of severity of cognitive decline according to the Mini-Mental State Examination. By inspecting Fig 2, it is apparent that the magnitude of impairment due to WMHs is invariant across the degree of cognitive decline.

In Table 3, the neuropsychological test results for patients with AD and VD, with and without WMHs, also are presented. There was no main effect of WMHs or dementia type in any test, and no significant interactions between WMHs and dementia type ($P>.10$). However, within the group of patients with AD, those with WMHs performed less well compared with those without WMHs in two tests: Tactile Identification of Objects (right hand) ($t=6.91$, $df=6$, $P<.001$) and Tactile Identification of Objects (left hand) ($t=2.07$, $df=6$, $P<.05$). Within the group of patients with VD, those with WMHs performed worse than those without WMHs in two tests: Object Assembly ($t=2.32$, $df=24$, $P<.05$) and Finger-tapping (left hand) ($t=1.76$, $df=25$, $P<.05$).

To explore further the relationship between the regional distribution of WMHs and neuropsychological functions, the demented group was dichotomized for every region of interest in those patients who had WMHs and those patients who did not have WMHs. For each region and test, the possible influence of WMHs on performance was analyzed with one-tailed t tests. An overview of these t tests is reported in Table 4. There were no effects whatsoever of WMHs on any neuropsychological test in several regions: the nonperiventricular left and right frontal, left and right temporal, left and right centrum semiovale, and nonperiventricular left and right posterior. However, in these regions, the frequency and amount of WMHs were relatively small. In the periventricular left and right frontal regions, as well as in the periventricular left and right posterior regions, however, there were many observations of WMHs, and the performance was significantly lower in those patients with, than in those without, WMHs in a number of neuropsychological tests: Block Design, Object Assembly, Simple Reaction Time, Finger-tapping (alternating hands), and Tactile Identification of Objects ($P<.05$).

Within the group of demented patients with WMHs, there was no significant correlation between the degree of WMHs of any brain region and the degree of cognitive decline, as assessed by the full-scale IQ ($r=.26$, $df=33$, $P>.10$) or by the Mini-Mental State Examination ($r=.12$, $df=44$, $P>.10$). Within diagnostic groups, there were no significant correlations between the degree of WMH and global cognitive decline either ($P>.10$).

In the group of healthy aged adults, no significant correlations were obtained between WMHs in specific regions and performance in specific tests, and in the group of demented patients, a few significant correlations were obtained. Tactile Identification of Objects (right hand) was significantly correlated to the degree of WMHs in three regions: left periventricular frontal ($r=.50$, $df=19$, $P<.05$), right periventricular frontal ($r=.48$, $df=19$, $P<.05$), and right periventricular posterior ($r=.52$, $df=19$, $P<.05$).

COMMENT

In this study, objective regional measurements of WMHs were made in patients whose conditions were diagnosed as demented and in healthy aged adults; the latter group was selected so that they might be considered as a group of successfully aged individuals.[44] The relative volume of WMHs was larger in the demented patients than in the healthy aged adults—this has been reported previously.[12,14-16,20] However, even in the healthy aged adults, WMHs were observed in some individuals.[4,9-12,15,16,20,21,28] Also, in agreement with prior research, was the finding that the relative volume of WMHs was larger in the patients with VD compared with that in the patients with AD.[12,13,20]

Although WMHs were common in the group of demented patients and not restricted in range, there was no indication of a negative relationship between the total degree of WMHs and global cognitive functioning, as assessed by the full-scale IQ from the Wechsler Adult Intelligence Scales–Revised or performance on the Mini-Mental State Examination. These results are in agreement with those found in prior research.[9-16,45] Grouping by type of dementia did not change this pattern of results. The degree of WMHs was, however, related to age and blood pressure. These results are also in agreement with those found in previous studies,[4] but not with an early pilot study by Bondareff and coworkers[17] in which six patients with AD were examined, or with a follow-up study by the same research group[18] in which 19 patients who had dementias with different origins were tested. These studies demonstrated a statistically significant relationship between the amount of WMHs and global cognitive performance, as assessed by the Mini-Mental State Examination and the Blessed Dementia Scale.

Most important, WMHs in specific regions seem to influence performance in specific neuropsychological tests, such as Finger-tapping, Tactile Identification of Objects, Simple Reaction Time, Block Design, and Object Assembly. In these tests, performance was more disturbed in demented patients with WMHs compared with that in demented patients without WMHs. In the healthy aged individuals, no negative influence of WMHs was observed neither globally nor specifically. It is interesting to note that those tests that showed differences due to WMHs in the demented patients were all time dependent to a considerable extent. The Finger-tapping Test measured the number of tappings in 10 seconds, and the Tactile Identification of Objects Test, as well as the Simple Reaction Time Test, relied on response latency, whereas the Block Design and Object Assembly tests assessed visuospatial manipulative performance with extra credits if performance was fast. Thus, WMHs may have slowed down certain basic cognitive processes. This interpretation is in line with the suggestion by Cummings[27] that tests sensitive to subcortical dysfunction should be used to study the possible influence of WMHs on cognitive functioning.

Subcortical dysfunction has also been suggested to have an effect on emotion.[27] Empirical support has been presented that blunted affect is related to WMHs in dementia.[20] In this study, however, no observations were made of emotional reactions or affective states. An interesting avenue for future investigations would be to examine the relationship between WMHs and affective states (eg, depression) in normal aging and dementia.

The relative cognitive impairment due to WMHs was mainly linked to periventricular brain regions, particularly anterior and posterior regions, where the watershed boundaries of blood circulation were located. In other regions of the brain (temporal, centrum semiovale, and nonperiventricular frontal and posterior), the frequency and degree of WMHs were sparse, which restricted the range of WMHs and made possible brain-behavior relationships difficult to detect. There was essentially no asymmetry between hemispheres in existence or degree of WMHs; this finding supports the hypothesis that WMHs are related to impaired blood perfusion.[4] The positive correlation between blood pressure and the degree of WMHs is another piece of evidence in favor of this hypothesis.

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Immunodiagnosis of Neurocysticercosis

Disappointing Performance of Serology (Enzyme-Linked Immunosorbent Assay) in an Unbiased Sample of Neurological Patients

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• To ascertain the reliability of serological diagnosis of neurocysticercosis in the everyday a priori situation of neurological consultation, the enzyme-linked immunosorbent assay test was used to predict the eventual diagnosis of neurocysticercosis in an unselected sample of 1064 consecutive neurological cases. Results showed 69% sensitivity and 71% specificity of the enzyme-linked immunosorbent assay test for the diagnosis of neurocysticercosis. In sharp contrast with publications that have proclaimed the excellent diagnostic performance of immunodiagnostic tests, our results suggest that identification of serum antibodies with standard enzyme-linked immunosorbent assay techniques is of little value when applied to a large and heterogeneous group of neurological patients in an endemic area of cysticercosis, and our results urge a reevaluation of currently used immunodiagnostic tests that are practiced in the serum of suspected cases.

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Neurocysticercosis (NCC) is a common parasitosis of the central nervous system in Latin America, Asia, and Africa.[1,2] In Mexico, NCC is the main cause of late-onset epilepsy[3] and a major source of several other neurological disorders.[1,4,5] There is general agreement that its precise diagnosis can be achieved in specialized institutions by the simultaneous use of imaging studies (ie, computed tomographic scans or magnetic resonance imaging) and cerebrospinal fluid (CSF) analysis, which includes immunological tests that are practiced in the CSF, where they apparently achieve a high reliability.[4-6] However, the design of a simple and dependable immunodiagnostic test in serum has long been sought as it would help medical and epidemiological studies. Unfortunately, and despite various attempts using a variety of procedures in conjunction with parasite extracts in semipurified antigen preparations, the total sum of results obtained reflect a confusing range of tests that vary in specificity and sensitivity.[6-12] Indeed, so great is the variation, that the feasibility of an accurate diagnosis of NCC through detection of serum antibodies has been called into question.[4,6,13-16] As a way to settle the issue, we decided to perform routine enzyme-linked immunosorbent assays (ELISAs) on serum samples that were obtained from neurological patients who were admitted to the National Institute of Neurology and Neurosurgery of Mexico, Mexico City, during a defined time interval but without knowledge of their presumptive or definitive neurological diagnosis at the time of the test. The sensitivity, specificity, and predictive value of the ELISAs for anticysticercus antibodies were compared a year later with the clinical records of the corresponding patients and their definitive diagnoses.

MATERIALS AND METHODS

Case Grouping and Sampling

Fresh serum samples that were obtained from 1064 patients were collected at random during a 6-month period at the clinical laboratory of the National Institute of Neurology and Neurosurgery of Mexico. The presumptive diagnosis was not known. All samples were tested in triplicate by the standard ELISA test for anticysticercus antibodies in serum. Two different methods of ELISA were tested: (1) 622 serum samples were screened by the alkaline phosphatase technique and (2) 442 serum samples were screened by the biotin-peroxidase technique.[16]

The diagnosis of every patient's condition whose serum was studied was disclosed from their medical records approximately 1 year after the samples were taken. Included were those cases in which a precise, final diagnosis was made with the aid of a computed tomographic scan, magnetic resonance imaging, surgery, CSF analysis, and multiple additional radiological and laboratory examinations; only patients in whom the abovementioned studies led to a clear diagnosis and in whom the diagnosis of NCC had been either confirmed or discarded beyond reasonable doubt were selected. All those cases in which imaging and CSF studies had not been practiced, because the treating physicians considered them to be unnecessary to reach a diagnosis, were discarded because the diagnosis had been based only on clinical criteria and the possibility of NCC had not been ruled out (ie, some cases of migraine, epilepsy, schizophrenia, depression, psychosomatic illness, etc). After the clin-

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Overall Correlation Between ELISA in Serum and Clinical Diagnosis of NCC in 678 Neurological Cases*

ELISA in Serum	Patients With Confirmed NCC	Patients With Diagnosis Other Than NCC	Total No. (%)
Positive	31 (*A*)	182 (*B*)	**213** (31)
Negative	14 (*C*)	451 (*D*)	**465** (69)
Total No. (%)	**45** (7)	**633** (93)	**678** (**100**)

*ELISA indicates enzyme-linked immunosorbent assay; NCC, neurocysticercosis. Sensitivity: $A/(A+C)=31/45$ (69%). Specificity: $D/(B+D)=451/633$ (71%). Precision: $(A+D)/(A+B+C+D)=482/678$ (71%). Prevalence: $(A+C)/(A+B+C+D)=45/678$ (7%). Positive predictive value: $A/(A+B)=31/213$ (15%). Negative predictive value: $D/(C+D)=451/465$ (97%).

ical evaluation of all cases, the results of ELISA for cysticercosis were disclosed.

From the original 1064 patients, 678 fulfilled the abovementioned criteria of an accurate neurological diagnosis based on studies that clearly defined the presence or absence of NCC. Additionally, the conditions of 21 patients were diagnosed as cases of NCC sequelae (parenchymal granulomas or calcifications) but without evidence of active NCC according to the criteria reported elsewhere[1,4,17]; these 21 cases were analyzed apart. The 678 cases were separated into one of two groups: group 1 comprised confirmed cases of active NCC (45 patients), and group 2 comprised confirmed cases of other neurological disorders, except NCC (633 patients).

Enzyme-Linked Immunosorbent Assay Tests for Serum Antibodies

The ELISA was employed for the serodiagnosis with the use of unfractionated vesicular fluid antigens of *Taenia solium* cysticerci.[10,13,16] The bound human immunoglobulins were then estimated with anti–human IgG coupled with alkaline phosphatase, or with biotinylated protein A, followed by streptavidin peroxidase.[16] All serum samples were diluted 1:20 or 1:1000 in phosphate-buffered saline solution (0.05 mol/L of sodium chloride for peroxidase or 0.01 mol/L of phosphate for phosphatase) and assayed in triplicate. On a given day, 50 to 100 problem serum samples were tested; in addition, eight to 12 negative control serum samples were included to provide an actualized cutoff value, and three to five positive control serum samples were included to validate reagents and procedures. A serum sample was considered to be positive when its ELISA optical density (OD) reading exceeded the mean negative control value +3 SDs.

The ELISA results were compared with the clinical diagnoses of every subject; the values of sensitivity, specificity, prevalence, and precision were obtained, along with positive and negative predictive values.

RESULTS

Of the total 678 serum samples, retrospective evaluation of medical records revealed 45 cases with NCC, ie, a prevalence of 7% in the sample. The remaining 633 serum samples belonged to patients with other neurological disorders (a comprehensive variety of neurological ailments, such as neoplasia, epilepsy, stroke, migraine, schizophrenia, dementia, vascular malformation, depression, head injury, infections, and degenerative disorders).

The Table summarizes the results, without distinction among different varieties of NCC (parenchymal, ventricular, or meningeal), nor the type of ELISA employed. A striking fact is that almost a third of all the serum samples were serologically positive (213 from 678), which is in contrast with the much lower number of confirmed NCC cases. Fifteen percent of the serologically positive cases were truly NCC. Only 31 of the 45 NCC cases were positive, while 451 of the 633 cases of non-NCC were negative. Thus, the sensitivity and specificity of the serological test was 69% and 71%, respectively. The positive predictive value of positive serology (15%) merely duplicated the global expectation derived from the overall prevalence value of 7%. This was not so for the negative predictive value, which was 97%. The overall precision value of the test was 71%.

Twenty-one additional patients had evidence, on imaging studies, of parenchymal brain-calcified granulomas; these lesions are usually a permanent sequela of parenchymal NCC that had been previously resolved by the host. Most patients from this group had epilepsy in which the cause was related to a granuloma secondary to their previous NCC that had been resolved, in some cases, several years earlier. The inclusion of these patients either in the group of NCC cases or in the group of non-NCC cases could have led to controversy and confusing interpretation of results; therefore, they were analyzed apart. Results of ELISA in these cases showed nine positives and 12 negatives, which gave values of 43% sensitivity if they were taken as NCC cases or 57% specificity if they were taken as non-NCC cases.

Among the group of patients with a diagnosis other than NCC, 38 had had a false-positive immunological test for NCC in the CSF analysis, either by complement fixation[18,19] or ELISA[6,20,21]; most of them had infectious, neoplastic, or hemorrhagic disorders within the subarachnoid space. The sero-ELISA for NCC in this subgroup showed 13 positives and 25 negatives, which gave 66% specificity in these cases.

When the type of ELISA employed was accounted for, serological results improved to some degree; ELISA with peroxidase was more efficient with regard to all parameters than ELISA with phosphatase (results not shown). In the best of cases, sensitivity reached values of 80%, and the positive predictive value was slightly increased to 16%. However, low specificity and many false positives prevailed with any technique in both active and inactive NCC.

The distribution of all ELISA values among the patients with NCC and the other neurological patients showed that, although the NCC cases had much higher ELISA titers than the non-NCC cases (29% vs 5%, respectively, were above an OD reading of 0.5), it was also clear that a high percentage of NCC cases (71%) were below an OD reading of 0.5 and could be confused with values registered for the other neurological patients, whose cutoff value for the confidence interval of 95% was precisely an OD reading of 0.5.

Results of ELISA in the cases that were excluded from the analysis showed 27% positives, ie, a value that was similar to the 31% positives in the cases included in this study, thus showing the unbiased inclusion criteria.

COMMENT

Serological (ELISA) immunodiagnosis showed a disappointing performance in detecting NCC cases in an unbiased sample of a large number of neurological patients. Our results are in contrast with those of other reports of high levels of sensitivity and specificity obtained with similar methodology by a number of laboratories, including our own,[8,10,12,16,22,23] and suggest that the diagnosis of NCC through identification of serum antibodies with standard ELISA techniques is unreliable when applied to the large and heterogeneous mass of neurological patients in an endemic area. Their significance in nonendemic areas is yet to be carefully assessed.

In this study, both sensitivity (69%) and specificity (71%) were far lower than expected. With an overall 7% prevalence of NCC in the sample, the predictive value of a positive serological result was only 15%. These low averages emerged mainly from the very high number of false-positive cases (29%) and from the high number of false-negative results (31%). Some of the difficulties in the development of a serological test of high predictive value for NCC are potentially soluble, while others seem hard to tackle.

The high number of false-positive results could result from several causes, ie, some biological and others methodological. It is possible that those patients without NCC but with positive serological tests were either infected with *T solium*, or they had been in previous contact with cysticerci, but NCC never developed; their antibodies, then, would reflect either intestinal taeniasis, muscle cysticercosis, or an immunological scar, but would provoke confusion when attempting to diagnose NCC. Also, the positive cutoff value for ELISA, as defined, may be too low, ie, the mean +3 SDs from the values obtained from healthy donors in the endemic area. This procedure was used when the ELISA test, applied herein, was first developed[16] and in every serum sample testing session in this study. Although they varied among sessions, the cutoff values never exceeded the OD value of 0.161 for alkaline phosphatase and of 0.525 for peroxidase. Consulting the distribution of OD values in the non-NCC neurological cases, we found that about a third exceeded these OD levels. Correction for this source of error is not easy, for example, choosing a lower cutoff OD value would drastically reduce the number of false-positive results to about 5% but would also further reduce the sensitivity of the test to about 30%. Another well-documented source of false-positive results is the presence of cross-reactive serum antibodies[13,24]; although not exhaustive, our results point to bacteria that are commonly found in hospitalized patients or to intestinal parasites as possibly being involved in false-positive results. Purification of specific antigens would be the obvious solution for cross-reactions. Recent investigations mention the identification of specific antigens of *T solium*[8,9,13,24,25]; other studies claim extremely high sensitivity and specificity results in Western blots with glycoproteins with an affinity for lentil lectin.[8,9,11] However, none of the latter assays have been tested in extensive field trials. A final possibility for explaining false positives is antigen sharing between *T solium* and the central nervous system tissue of patients; cysticerci are extremely complex organisms that are equipped with nerves, muscle, collagen, and a number of other biological molecules and structures that are widely distributed and preserved in the animal kingdom. If damage to the central nervous system occurs in the development of a neurological disease, the autoantibodies that are induced could cross-react with parasite components. Although this suggestion is speculative, it would provide an immediate explanation for the huge difference in the prevalence of serological positivity in the open population of Mexico (about 3%)[7] and in the neurological population of this study (about 30%). For practical purposes, such cross-reactive autoantibodies would complicate the serological diagnosis of NCC among neurological patients and provide a stimulus for the development of more precise procedures.

The low sensitivity found in this study (69%), as opposed to the very high values reported in the literature (with many values close to 100%),[8-10] has also a dual methodological and biological origin. The usual procedure to evaluate a newly developed serological method is to test its ability to discriminate among well-defined control positive and negative serum samples. We believe this procedure is usually biased by a tendency to select the most representative samples of both control serum samples: those most positive and those most negative. Thus, the variables of the method (cutoff values, dilutions, enzymes, buffers, etc) are streamlined to best meet the particular problem of distinguishing the archetypes, but not the heterogeneous masses of neurocysticercotic and nonneurocysticercotic neurological patients with overlapping distributions of serological reactivity. In our case, the standard procedure ignored that many neurocysticercotic patients do not have measurable circulating antibodies to cysticerci,[27,28] whereas many other subjects could have either cross-reactive antibodies or anticysticercus antibodies without suffering NCC. Biologically, then, deficient sensitivity of serological tests stems from those patients in whom the immune reaction against the parasite takes place only within the subarachnoid space with local production of immunoglobulins and negligible amounts of antibodies in peripheral blood,[1,6,8,9,19] or we speculate from well-established host-parasite relationships that are free from immunological confrontation, either because of specific immunodepression[28,29] or other less-defined forms of peaceful endurance between parasite and host.[27]

In contrast, negative serology to cysticercus antigens turned out to have a high predictive value for noncysticercotic neurological ailments (97%). Thus, a negative serology would practically rule out NCC from diagnostic considerations in most neurological cases. However, this attractive result should also be taken cautiously because this high value derives mostly from the high prevalence of nonneurocysticercotic cases (93%) in our sample and not, unfortunately, from scarcity of patients with NCC without antibodies in peripheral blood, which was, in fact, quite common (31%).

We conclude that currently available serological procedures are not satisfactory for the positive diagnosis of NCC in the realistic situation of confronting the heterogeneous mass of neurological ailments in an endemic area. Before diagnostic procedures that detect anticysticercus antibodies in serum are further applied, we suggest that they should be assessed in an unbiased and massive design as the one used here, rather than via the testing of panels of a limited number of previously established clearly positive or clearly negative serum samples.

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ANNOUNCING

Acute migraine pain relief...

From a nasal spray

Mead Johnson Laboratories
introduces the only nasal spray analgesic

New STADOL® NS™

(butorphanol tartrate) Nasal Spray

A Potent Analgesic

- Synthetically derived opioid analgesic with sedative properties*
- Efficacy comparable to IM meperidine
- Onset of pain relief within 15 minutes[1]

Effective in Acute Pain

- Demonstrated efficacy in relief of acute migraine pain[1]
- Relieved the acute pain of migraine unresponsive to specific abortive agents[1]
- Also proven effective in the relief of acute pain following invasive surgical procedures[2]
- The most frequently reported adverse effects are: somnolence (43%), dizziness (19%), and nausea/vomiting (13%)

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A Convenient New Dosing Form

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- Not a federally controlled substance

Simple, Flexible Dosing

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- An additional 1-mg dose may be taken in 60 minutes if needed†
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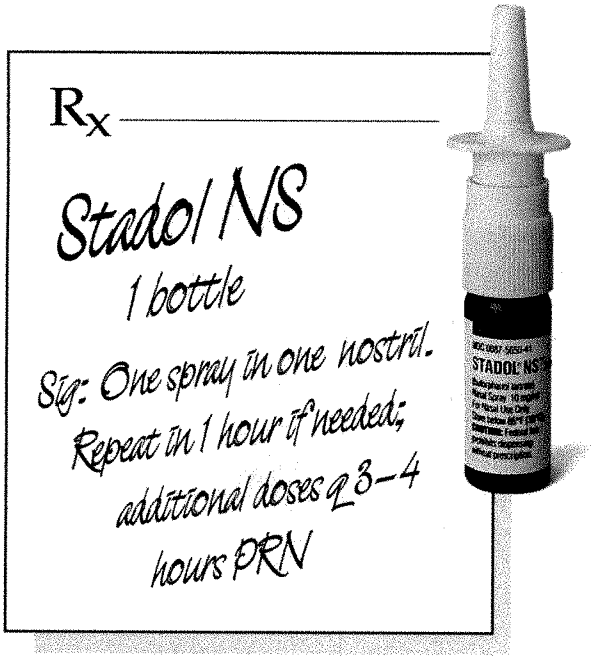

Rx

Stadol NS

1 bottle

Sig: One spray in one nostril.
Repeat in 1 hour if needed;
additional doses q 3–4
hours PRN

Acute Pain Relief, Delivered in Minutes

*Patients should not perform potentially hazardous tasks (eg, driving, operating machinery). Alcohol should not be consumed while using butorphanol.

†Depending on the severity of pain, an initial dose of 2 mg (one spray in each nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs.

Please see next page for brief summary of prescribing information.

STADOL® NS™

(butorphanol tartrate) Nasal Spray

Acute Pain Relief, Delivered in Minutes

Brief Summary

INDICATIONS

STADOL® NS™ (butorphanol tartrate) Nasal Spray is indicated for the management of pain when the use of an opioid analgesic is appropriate.

CONTRAINDICATIONS

STADOL NS is contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride.

WARNINGS

Patients Dependent on Narcotics

Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

PRECAUTIONS

Head Injury and Increased Intracranial Pressure

As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control

Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease

In patients with severe hepatic or renal disease the initial dosage interval for STADOL NS should be increased to 6-8 hours until the response has been well characterized. Subsequent doses should be determined by patient response rather than being scheduled at fixed intervals.

Cardiovascular Effects

Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Drug Interactions

Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (cimetidine, erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

The fraction of STADOL NS absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if STADOL NS is administered concomitantly with, or immediately following, a nasal vasoconstrictor.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Use in Ambulatory Patients

Drowsiness and dizziness related to the use of butorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc.). Patients should be told to use caution in such activities until their individual responses to butorphanol have been well characterized.

Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects.

Patients should be instructed on the proper use of STADOL NS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of butorphanol has not been adequately evaluated.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/sq.m.) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/sq.m.) subcutaneous dose.

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation.

Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. Pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/sq.m.) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (5.1 mg/sq.m.) and 60 mg/kg/oral (10.2 mg/sq.m.) also showed higher incidences of post implantation loss in rabbits.

Labor and Delivery

STADOL NS is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

Nursing Mothers

Butorphanol has been detected in milk following administration of STADOL Injectable to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 microgram/liter of milk in a mother receiving 2 mg IM four times a day).

Although there is no clinical experience with the use of STADOL NS in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

Pediatric Use

Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use

Initially a 1 mg dose of STADOL NS should generally be used in geriatric patients and 90-120 minutes should elapse before deciding whether a second 1 mg dose is needed.

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65. Elderly patients may be more sensitive to its side effects. Results from a long-term clinical safety trial suggest that elderly patients may be less tolerant of dizziness due to STADOL NS than younger patients.

ADVERSE REACTIONS

A total of 2446 patients were studied in butorphanol clinical trials. Approximately half received STADOL Injectable with the remainder receiving STADOL NS. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short- and long-term clinical trials in patients receiving butorphanol by any route and from post-marketing experience with STADOL Injectable. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo treated patients in controlled trials.

REACTIONS

The most frequently reported adverse experiences across all clinical trials with STADOL Injectable and STADOL NS were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with STADOL NS only, nasal congestion (13%) and insomnia (11%) were frequently reported.

The following adverse experiences were reported at a frequency of 1% or greater, and were considered to be probably related to the use of butorphanol:

BODY AS A WHOLE: asthenia/lethargy*, headache*, sensation of heat

CARDIOVASCULAR: VASODILATION*, PALPITATIONS

DIGESTIVE: ANOREXIA*, CONSTIPATION*, dry mouth*, nausea and/or vomiting (13%), stomach pain

NERVOUS: anxiety, confusion*, dizziness (19%), euphoria, floating feeling, INSOMNIA (11%), nervousness, paresthesia, somnolence (43%), TREMOR

RESPIRATORY: BRONCHITIS, COUGH, DYSPNEA*, EPISTAXIS*, NASAL CONGESTION (13%), NASAL IRRITATION*, PHARYNGITIS*, RHINITIS*, SINUS CONGESTION*, SINUSITIS, UPPER RESPIRATORY INFECTION*

SKIN AND APPENDAGES: sweating/clammy*, pruritus

SPECIAL SENSES: blurred vision, EAR PAIN, TINNITUS*, UNPLEASANT TASTE* (also seen in short-term trials with STADOL® NS™ [butorphanol tartrate] Nasal Spray)

(Reactions occurring with a frequency of 3-9% are marked with an asterisk.* Reactions reported predominantly from long-term trials with STADOL NS are CAPITALIZED.)

The following adverse experiences were reported with a frequency of less than 1%, in clinical trials or from post-marketing experience and were considered to be probably related to the use of butorphanol.

CARDIOVASCULAR: hypotension

NERVOUS: abnormal dreams, agitation, *drug dependence*, dysphoria, hallucinations, hostility

SKIN AND APPENDAGES: rash/hives

UROGENITAL: impaired urination

(Reactions reported only from post-marketing experience are *italicized.*)

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term STADOL NS trials and from post-marketing experiences under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

BODY AS A WHOLE: edema

CARDIOVASCULAR: hypertension

NERVOUS: *convulsion*, *delusions*, depression

RESPIRATORY: *apnea*, shallow breathing

(Reactions reported only from post-marketing experience are *italicized.*)

DRUG ABUSE AND DEPENDENCE

Although the mixed agonist-antagonist opioid analgesics, as a class, have lower abuse potential than morphine, all such drugs can be and have been reported to be abused.

Chronic use of STADOL Injectable has been reported to result in mild withdrawal syndromes, and reports of overuse and self-reported addiction have been received.

Among 161 patients who used STADOL NS for 2 months or longer approximately 3% had behavioral symptoms suggestive of possible abuse. Approximately 1% of these patients reported significant overuse. Symptoms such as anxiety, agitation, and diarrhea were observed. Symptoms suggestive of opioid withdrawal occurred in 2 patients who stopped the drug abruptly after using 16 mg a day or more for longer than 3 months.

Special care should be exercised in administering butorphanol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is necessary, such patients should be closely supervised.

OVERDOSAGE

Clinical Manifestations

The clinical manifestations of overdose are those of opioid drugs, the most serious of which are hypoventilation, cardiovascular insufficiency and/or coma.

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment

The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

DOSAGE AND ADMINISTRATION

Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, patients with hepatic or renal disease or in labor requires extra caution (see PRECAUTIONS). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60-90 minutes, an additional 1 mg dose may be given.

The initial two dose sequence outlined above may be repeated in 3-4 hours as needed.

Depending on the severity of the pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients single additional 2 mg doses should not be given for 3-4 hours.

Safety and Handling

STADOL NS is an open delivery system with increased risk of exposure to health care workers.

In the priming process, a certain amount of butorphanol may be aerosolized, therefore the pump sprayer should be aimed away from the patient or other people or animals.

The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED

STADOL NS is supplied in a child-resistant prescription vial containing a metered-dose spray pump and protective clip with dust cover, a bottle of nasal spray solution, and a patient instruction leaflet. On average, one bottle will deliver 14-15 doses if no repriming is necessary.

NDC 0087-5650-41: 10 mg per mL, 2.5-mL bottle.

Storage Conditions

Store below 86°F (30°C). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CAUTION: Federal law prohibits dispensing without prescription.

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2. Data on file, Bristol-Myers Squibb Company.

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Sleep Disturbance, Depression, and Lesion Site in Patients With Multiple Sclerosis

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• We examined the prevalence of sleep problems in a sample of patients with mild but clinically definite multiple sclerosis (n = 143) and sought to determine whether there was a relationship between the presence of sleep complaints and the level of depression. As magnetic resonance imaging scans were available for a subsample of the patients with multiple sclerosis (n = 117), we also wanted to determine whether there was a relationship between the site of the lesion and the presence of sleep difficulties. The prevalence of sleep difficulties was three times higher in the patients with multiple sclerosis than the control group (25.2% vs 8.2%). Moreover, the presence of sleep complaints was associated with higher levels of depression. Three lesion sites that subserve supplemental motor areas were significantly related to the presence of sleep complaints. These findings suggest that, for some patients with MS, sleep disturbance and accompanying increases in depression may be a function of the lesion site resulting in nocturnal spasms.

(*Arch Neurol.* 1992;49:641-643)

Although clinically recognized, problems of sleep initiation and maintenance in patients with multiple sclerosis (MS) have only recently been investigated in terms of extent, type, or clinical implications.[1] Because fatigue is a common complaint among patients with MS, it is important to determine whether disrupted sleep cycles contribute to this complaint.[2] Sleep disturbance is also common in patients with depression.[3] For patients with MS, resolution of this question may have direct clinical ramifications. However, it has yet to be determined whether sleep disturbance or depression is the causative agent. For example, if sleep disruption does occur, a palliative treatment program may be created to lessen the general fatigue, or perhaps depression, experienced by these patients. Therefore, we sought to determine whether patients with MS had more complaints regarding sleep pattern compared with healthy control subjects. We also sought to determine whether patients with MS with sleep disturbance had elevated levels of depression compared with other patients with MS. As magnetic resonance imaging (MRI) scans were available for the majority of these patients, we also wanted to determine whether disruptions in sleep were related to the site of the lesion. In particular, recent studies have suggested that patients with MS are often awakened during sleep due to periodic limb movement disorder.[4] Such movements may be related to demyelination of axons involved in motor movements.

SUBJECTS AND METHODS

Subjects

The subjects were recruited from The University of British Columbia MS clinic and met the following criteria: (1) diagnosis of clinically definite MS with a relapsing/remitting course[5]; (2) disease in remission at the time of assessment; (3) no concurrent medical diseases; (4) no history of psychiatric illness before diagnosis of MS; (5) no history of alcohol or other drug abuse; (6) medication free at the time of testing; (7) aged younger than 40 years at the time of diagnosis (mean age, 30.7 years) and aged younger than 50 years at the time of assessment; and (8) a score of less than 6.0 on the Kurzke Extended Disability Scale (mean score, 2.14).[6] Whenever possible, each subject was asked to recruit a same-sex unrelated control subject with a similar socioeconomic background. The resulting samples consisted of 143 patients with MS (40 men and 103 women) and 70 control subjects (21 men and 49 women). As expected, these two groups did not differ in age (mean ages, 35.7 years and 35.1 years for the MS and control groups, respectively; $t = .41$) or educational background (mean number of years of education, 13.5 years and 13.4 years for the MS and control groups, respectively; $t = .61$).

Materials

As part of a comprehensive psychological battery, each subject completed the Minnesota Multiphasic Personality Inventory. From this inventory, 10 items were found that related to sleep patterns: sleep initiation (two items), sleep maintenance (two items), sleep outcome (one item), somnambulism (one item), nightmares (one item), sleep reversal (one item), and disturbance of sleep cycle due to anxiety (two items). The frequency of endorsement for each of these items was compared between the two groups with use of χ^2 analysis. Subsequently, items for which differences were found at $P \leq .1$ were summed to determine whether the same subjects were endorsing the significant items. This score was used accordingly as an estimate of sleep disturbance.

In addition, each subject completed a Beck Depression Inven-

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Table 1.—Endorsement of Sleep Items by Normal Controls and Patients With Multiple Sclerosis (MS)

	% Endorsement by Group		
Area	Normal Controls (n = 70)	Patients With MS (n = 143)	χ^2
Sleep initiation	23.0	38.4	4.57*
	61.6	67.8	0.57
Maintenance	50.7	63.3	2.70†
	9.5	28.8	9.50*
Sleep outcome	32.4	47.6	4.04*
Somnambulism	9.5	8.2	0.00
Nightmares	2.7	9.5	2.47
Sleep reversal	5.4	4.1	0.00
Disturbance of cycle	8.1	15.8	1.88
	27.0	22.4	0.34

*$P \leq .05$.
†$P \leq .10$.

tory (BDI). As only one of the 21 items in this inventory is directly related to sleep, this instrument was thought to be a relatively sleep-independent measure of depression. Specifically, a maximum of three points of a possible 63 are related to sleep disturbance. Therefore, the patients with MS and the control subjects with and without sleep disturbance were compared on the BDI by means of a two-factor analysis of variance procedure. Subsequently, the groups were compared with use of Tukey's post hoc test ($P \leq .05$). All psychological testing was done on the same day.

Magnetic Resonance Imaging Scans

Among the 143 patients with MS, MRI scans were obtained for 117 patients. The scans were obtained on the same day on which the psychological assessment was performed. All subjects underwent scanning (Picker International Cyrogenic MR 2000 scanner, Picker International Cyrogenic, Cleveland, Ohio) at 0.15 T. Images were obtained with use of a simultaneous multiple 12-section spin-echo sequence with a repetition time of 2000 milliseconds and echo times of 60 and 120 milliseconds in the transverse and sagittal planes, respectively. One of us (D.L.) reviewed these sections and determined whether lesions were present at 50 predetermined sites. Scans were also available for the control subjects. However, the incidence of lesions at sites other than the periventricular regions was essentially zero. Therefore, these normal scans were not used in subsequent analyses, as their inclusion would artificially inflate the χ^2 values. For the periventricular regions, a separate analysis was done for the control subjects if a difference was found from the patients with MS. The selection of the 50 sites was based on our previous experience with patients with MS and included the white matter associated with the medulla; midbrain; pons; cerebellum; thalamus; basal ganglia; insula; internal capsule; temporal, parietal, occipital, and frontal lobes; and the corpus callosum. The presence of a lesion at a specific site was correlated with the sleep disturbance score with use of χ^2 analysis. To reduce the Type I error rate but still preserve statistical sensitivity, the α level was set at $P \leq .01$. Specifically, as the study was truly exploratory, a Type I error was considered a less drastic form of error than a Type II error.

RESULTS

The results in terms of sleep disturbance are summarized in Table 1, and the actual items are listed in Table 2. The control and MS groups differed significantly on three items, with the MS group consistently reporting more complaints. These items were as follows: (1) Most nights I go to bed without thoughts or ideas bothering me (sleep initiation). (2) My sleep is fitful and disturbed (sleep maintenance). (3) I wake up fresh and rested most mornings (sleep outcome). For a fourth item (I am easily awakened by noise), there was a trend ($P \leq .10$) for the MS group to endorse this item more frequently. These four items are measures of the sleep process. As the two groups did not differ on the remaining six items, these items were excluded from further analysis.

Table 2.—Ten Identified MMPI* Items Associated With Sleep Disorder and Area of Sleep Problem

Area	Item
Sleep initiation	(1) Most nights I go to sleep without thoughts or ideas bothering me. (2) Sometimes I become so excited that I find it hard to get to sleep.
Sleep maintenance	(1) I am easily awakened by noise. (2) My sleep is fitful and disturbed.
Sleep outcome	(1) I wake up fresh and rested most mornings.
Somnambulism	(1) I have been told that I wake during sleep.
Nightmares	(1) I have nightmares every few nights.
Sleep reversal	(1) I can sleep during the day but not at night.
Disturbance of sleep cycle	(1) I have had periods in which I lost sleep over worry. (2) I have had periods when I felt so full of pep that sleep did not seem necessary for days at a time.

*MMPI indicates Minnesota Multi-Phasic Personality Inventory.

Table 3.—Distribution of Sleep Scores for Normal Controls and Patients With Multiple Sclerosis (MS)

	Score, %					
Group	0	1	2	3	4	Kendall's Tau
Normal controls	27.4	37.0	27.4	8.2	0	0.22
MS	13.3	32.9	28.7	11.2	14.0	$P \leq .0002$

For the four items specified above, the scores were summed to generate a sleep score (ie, ranging from 0 through 4, with 0 implying no sleep complaints and 4 reflecting endorsement of all four items). The distribution by group of these scores is given in Table 3. From these data, it is clear that the patients with MS reported more disruption of sleep than control subjects, with only 8.2% of the control subjects scoring 3 and 25.2% of the patients with MS scoring 3 or 4.

When the control subjects and patients with MS were subdivided in terms of sleep disturbance (defined as a sleep score ≥ 3), and compared with regard to the BDI, a significant group effect ($F[1,211]=9.65$, $P \leq .002$) and a significant sleep effect ($F[1,211]=17.35$, $P \leq .001$) were found. The mean (SD) BDI scores for the four groups were as follows: (1) control subjects with no sleep complaints, 3.1 (3.2); (2) control subjects with sleep complaints, 7.3 (6.4); (3) patients with MS with no sleep complaints, 6.2 (5.2); and (4) patients with MS with sleep complaints, 11.2 (5.2). The results of Tukey's post hoc test indicated that

(1) the control subjects with no sleep complaints had significantly lower BDI scores than the other three groups and (2) the MS group with sleep complaints had significantly higher BDI scores than the other three groups. Moreover, this latter finding could not be explained by endorsement of the sleep questions on the BDI, as the overall difference between the two MS groups was 5.0 points. With respect to the clinical level of depression and BDI scores, the control subjects and the patients with MS with sleep complaints fall in the reference range (scores of 0 to 10), while the MS group with sleep complaints falls in the palpable range (scores of 10 to 20) but not the clinical range (scores >20).

For the MRI lesion analysis, three sites were identified for which a significant relationship was found between the site of the lesion and the sleep score. These regions were the right and left frontal white matter as imaged on the supraventricular section and the deep white matter of the right insula ($\chi^2=24.0$, 13.4, and 13.6, respectively; $df=4$; $P\leq.01$). For patients with lesions at these sites, 12 of 24 with lesions in the right frontal region had sleep complaints (sleep scores of 3 or 4), 11 of 24 patients with lesions in the left frontal region had sleep complaints, and six of 10 patients with lesions in the deep white region of the insula had sleep complaints. With respect to patients with sleep complaints, 17 (65%) of 26 had a lesion at one or more of these three sites. Conversely, these 17 patients represent 50% of the 34 patients with lesions at one or more of these sites. Finally, when these patients with sleep complaints and lesions are removed from the MS sample, the incidence of sleep complaints is almost equivalent to that of the control population (ie, 9% in the MS sample and 8.2% in the control sample).

COMMENT

Our results are consistent with those of other clinical reports in that sleep difficulties are common in patients with MS (25.2%)[1,2] and that, for our sample of patients with MS, sleep complaints were three times as frequent as in a sample of control subjects. In addition, sleep difficulties were associated with significant increases in level of depression in the MS group. Given the mild clinical presentation of these patients in terms of disability scores (mean, 2.14), our study, in all probability, underestimates the incidence and severity of sleep disruption in the general population of patients with MS. At this time, there are few published studies regarding sleep disturbance in MS, although a number of abstracts have recently been published.[1,2,4,7] These studies suggest that sleep disturbance may be associated with depression, fatigue, spasticity, bladder difficulties, and periodic leg movements. Hence, one may argue that primary symptoms of MS (eg, spasticity and bladder problems) may disrupt the sleep cycles, resulting in increased levels of depression or fatigue. Clearly, such a hypothesis is worth exploring due to the disabling but, perhaps, treatable effects of fatigue and depression, especially for patients with mild disease in whom these secondary effects may be as debilitating as the primary symptoms of MS.

With respect to such a hypothesis, the MRI findings suggest that the site of the disease process may be related to the presence of sleep complaints. Lesions in three regions, namely, the right and left frontal supraventricular white matter and the deep white matter of the right insula, were found to be related to the presence of sleep complaints. Axons in these areas subserve supplemental motor areas in terms of neuronal functions.[8,9] Although speculative, it may be argued that disruption of the normal action potential conductance may cause periodic limb movements during sleep, resulting in sleep disruption. For example, Potolicchio et al[4] have reported periodic limb movements in seven of 11 patients with MS studied in their sleep laboratory. Similarly, in our study, when patients with lesions in any of the above-mentioned three regions and sleep complaints are removed from the sample, the incidence of sleep complaints in the MS sample is comparable with that in the control subjects. These two findings suggest that for a subgroup of patients with MS, sleep disturbance is related to lesion site, while for the remainder, sleep disturbance may be a normal variation or at least not associated with MS. To examine these speculations, the next step would be to begin systematic sleep studies with MRI scans to determine whether patients with lesions in these specific sites are more prone to sleep disturbance, particularly periodic leg movements. If these studies are successful, then clinical trials for amelioration could be undertaken. Successful treatment should yield reductions in levels of depression and perhaps fatigue.

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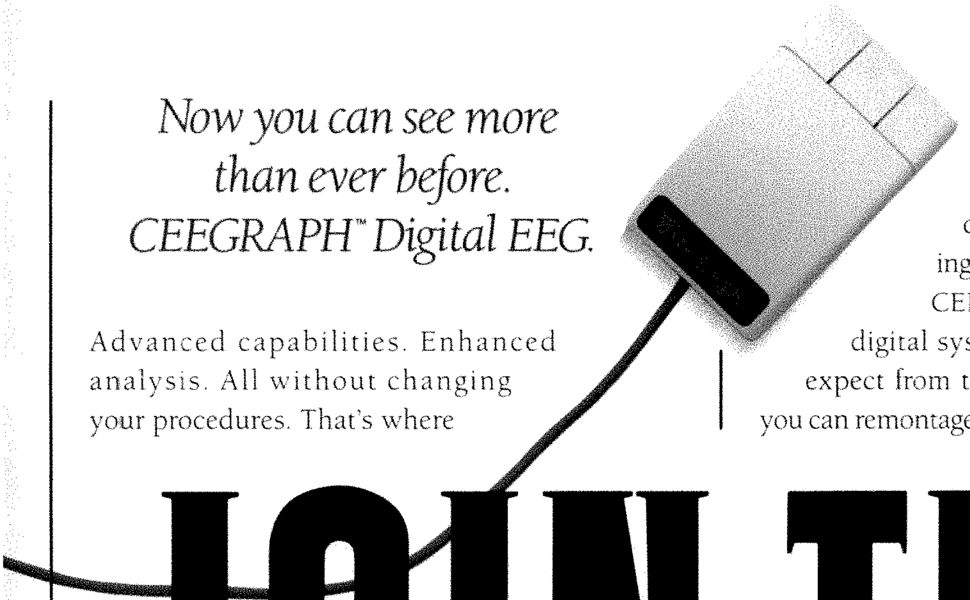

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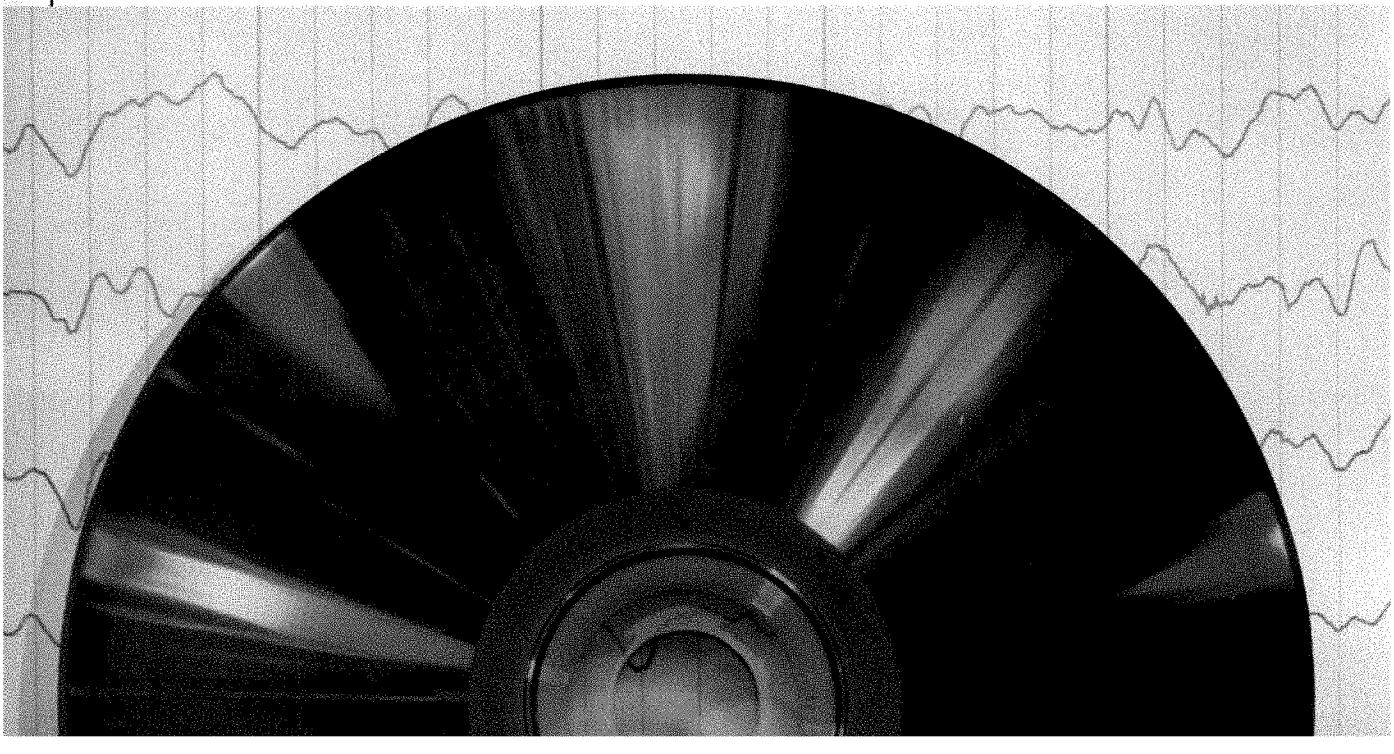

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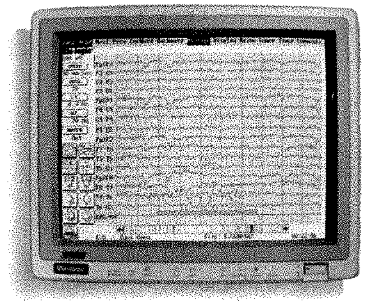

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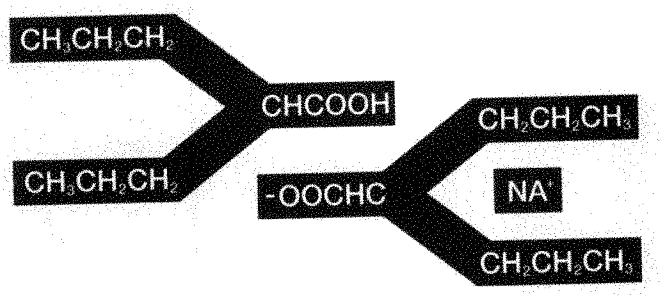

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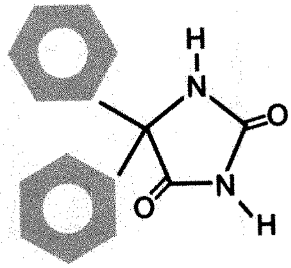

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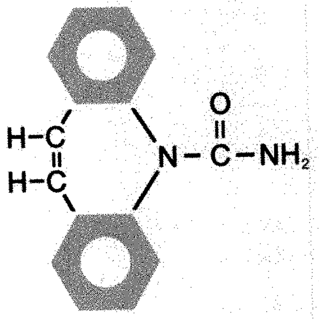

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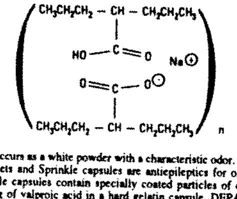
> **WARNING:**
>
> HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTI-CONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF SEIZURE CONTROL SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.
>
> THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

DESCRIPTION

Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium has the following structure:



Divalproex sodium occurs as a white powder with a characteristic odor.

DEPAKOTE tablets and Sprinkle capsules are antiepileptics for oral administration. DEPAKOTE Sprinkle capsules contain specially coated particles of divalproex sodium equivalent to 125 mg of valproic acid in a hard gelatin capsule. DEPAKOTE tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg, or 500 mg of valproic acid.

Inactive Ingredients

125 mg Sprinkle capsules: cellulosic polymers, D&C Red No. 28, FD&C Blue No. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.

DEPAKOTE tablets: cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, and vanillin.

In addition, individual tablets contain:
125 mg tablets: FD&C Blue No. 1 and FD&C Red No. 40.
250 mg tablets: FD&C Yellow No. 6 and iron oxide.
500 mg tablets: D&C Red No. 30, FD&C Blue No. 2, and iron oxide.

CLINICAL PHARMACOLOGY

Divalproex sodium is an antiepileptic agent which dissociates to the valproate ion in the gastrointestinal tract. The mechanism by which valproate exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA).

Equivalent oral doses of DEPAKOTE (divalproex sodium) products and DEPAKENE (valproic acid) capsules deliver equivalent quantities of valproate ion systemically. However, the rate of valproate ion absorption may vary with the conditions of use (eg, fasting or postprandial) and the method of administration (eg, whether the contents of the capsule are sprinkled on food or the capsule is taken intact).

When subjects are in a fasting state, peak plasma concentrations of valproate ion are observed approximately 3 to 4 hours following administration of all DEPAKOTE products.

Experiments indicate that feeding can influence the rate of systemic absorption of valproate. In studies in which the contents of DEPAKOTE (divalproex sodium) Sprinkle capsules were sprinkled on applesauce, feeding was found to delay the time to peak plasma concentration by approximately 1.5 hours.

Compared to DEPAKOTE tablets, however, DEPAKOTE Sprinkle capsules (in the fasting state) exhibit a slower rate of absorption, resulting in lower peak plasma concentrations (ie, fluctuations between minimum and maximum plasma valproate concentrations are attenuated).

While absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate in chronic use is not affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.

Accordingly, coadministration of oral valproate products with food and substitution among the various DEPAKOTE and DEPAKENE formulations should cause no clinical problems (see DOSAGE AND ADMINISTRATION). Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

The plasma half-life of valproate is typically in the range of 6 to 16 hours. Half-lives in the lower part of the range are usually found in patients taking other antiepileptic drugs capable of enzyme induction.

Valproate is primarily metabolized in the liver. The major metabolic routes are glucuronidation, mitochondrial beta oxidation, and microsomal oxidation. The major metabolites formed are the glucuronide conjugate, 2-propyl-3-keto-pentanoic acid, and 2-propyl-hydroxypentanoic acids. Other unsaturated metabolites have been reported. The major route of elimination of these metabolites is in the urine.

Patients on monotherapy will generally have longer half-lives and higher concentrations of valproate at a given dosage than patients receiving polytherapy. This is primarily due to enzyme induction caused by other antiepileptics, which results in enhanced clearance of valproate by glucuronidation and microsomal oxidation. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

The therapeutic range is commonly considered to be 50 to 100 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.[5] Valproate is highly bound (90%) to plasma proteins in the therapeutic range; however, protein binding is concentration-dependent and decreases at high valproate concentrations. The binding is variable among patients and may be affected by fatty acids or by highly bound drugs such as salicylate. Some clinicians favor monitoring free valproate concentrations, which may more accurately reflect CNS penetration of valproate. As yet, a consensus on the therapeutic range of free concentrations has not been established; however, monitoring total and free valproate may be informative when there are changes in clinical status, concomitant medication, or valproate dosage.

INDICATIONS AND USAGE

DEPAKOTE (divalproex sodium) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE WARNINGS FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DIVALPROEX SODIUM SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia, and vomiting. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKOTE products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risks. Above this age group, experience has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage in Pregnancy: ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.[1]

OTHER CONGENITAL ANOMALIES (EG, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

ANIMAL STUDIES ALSO HAVE DEMONSTRATED VALPROATE INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

PRECAUTIONS

Hepatic Dysfunction: See BOXED WARNING, CONTRAINDICATIONS AND WARNINGS.

General: Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (eg, low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. Asymptomatic elevations of ammonia are more common and when present require more frequent monitoring. If clinically significant symptoms occur, DEPAKOTE therapy should be modified or discontinued.

Since valproate may interact with concurrently administered antiepileptic drugs, periodic plasma concentration determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See DRUG INTERACTIONS).

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Information for Patients: Since DEPAKOTE products may produce CNS depression, especially when combined CNS depressants (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

The specially coated particles in DEPAKOTE Sprinkle capsules have been observed in the stool, but this occurrence has not been associated with clinically significant effects.

Drug Interactions: Valproate may potentiate the action of CNS depressants (ie, alcohol, benzodiazepines, etc).

The concomitant administration of valproate with drugs that exhibit extensive protein binding (eg, aspirin, carbamazepine, dicumarol, and phenytoin) may result in alteration of serum drug concentrations.

There is evidence that valproate can cause an increase in serum phenobarbital concentrations by impairment of nonrenal clearance. This phenomenon can result in severe CNS depression. The combination of valproate and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone is metabolized to a barbiturate and, therefore, may also be involved in a similar or identical interaction.

There have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. Most reports have noted a decrease in total plasma phenytoin concentration. However, increases in total plasma phenytoin concentration, however, increases in total phenytoin serum concentration have been reported. An initial fall with subsequent increase in total phenytoin concentrations has also been reported. In addition, a decrease in total serum phenytoin with an increase in the free vs. protein bound phenytoin concentrations has been reported. The dosage of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide concentrations. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Caution is recommended when valproate is used with drugs affecting coagulation (eg, aspirin, warfarin). See ADVERSE REACTIONS.

Evidence suggests that there is an association between the use of certain antiepileptics and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing antiepileptics effectively lower plasma concentrations of the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. While valproate is not a significant enzyme inducer, and, therefore, would not be expected to decrease concentrations of steroid hormones, clinical data about the interaction of valproate with oral contraceptives is minimal.[2]

Carcinogenesis: Valproic acid was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 80, and 170 mg/kg/day for two years. A vari plasms were observed in both species. The chief findings were a statistically increase in the incidence of subcutaneous fibrosarcomas in high dose male ra valproic acid and a statistically significant dose-related trend for benign pulmo mas in male mice receiving valproic acid. The significance of these findings fo unknown.

Mutagenesis: Studies of valproate have been performed using bacterial and systems. These studies have provided no evidence of a mutagenic potential for

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs de reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have s up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT PROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCT FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy: Pregnancy Category D: See WARNINGS.

Nursing Mothers: Valproate is excreted in breast milk. Concentrations in have been reported to be 1-10% of serum concentrations. It is not known what would have on a nursing infant. Caution should be exercised when divalproex administered to a nursing woman.

ADVERSE REACTIONS

Since divalproex sodium has usually been used with other antiepileptic drugs, it i ble, in most cases, to determine whether the following adverse reactions can be divalproex sodium alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation are nausea, vomiting, and indigestion. These effects are usually transient and rar discontinuation of therapy. Diarrhea, abdominal cramps, and constipation reported. Both anorexia with some weight loss and increased appetite with w have also been reported. The administration of delayed-release divalproex so result in reduction of gastrointestinal side effects in some patients.[3]

CNS Effects: Sedative effects have occurred in patients receiving valproate occur most often in patients receiving combination therapy. Sedation usually a reduction of other antiepileptic medication. Tremor (may be dose-related), hallu ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, and incoordination. Rare cases of coma have occurred in patients receiving valpr or in conjunction with phenobarbital. In rare instances encephalopathy with developed shortly after the introduction of valproate monotherapy without ev hepatic dysfunction or inappropriate plasma levels; all patients recovered after was withdrawn.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pru thema multiforme, and Stevens-Johnson syndrome. A case of fatal epidermal n has been reported in a 6 month old infant taking valproate and several other co medications.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperacti behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: Thrombocytopenia and inhibition of the secondary phase of aggregation may be reflected in altered bleeding time, petechiae, bruising, hema mation and frank hemorrhage (see PRECAUTIONS — *General* and *Drug Inter* Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinoph mia including macrocytic with or without folate deficiency, bone marrow suppres acute intermittent porphyria.

Hepatic: Minor elevations of transaminases (eg, SGOT and SGPT) and LDH quent and appear to be dose related. Occasionally, laboratory test results include in serum bilirubin and abnormal changes in other liver function tests. These res reflect potentially serious hepatotoxicity (see WARNINGS).

Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, gal and parotid gland swelling. Abnormal thyroid function tests (see PRECAUTIONS

Pancreatic: Acute pancreatitis, including fatalities.

Metabolic: Hyperammonemia (see PRECAUTIONS), hyponatremia, and inap ADH secretion.

Decreased carnitine concentrations have been reported although the clinical r is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a pa preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis.

Special Senses: Hearing loss, either reversible or irreversible, has been reporte ever, a cause and effect relationship has not been established.

Other: Edema of the extremities, lupus erythematosus, and fever.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. ties have been reported.

The benefit of gastric lavage or emesis will vary with the time since ingestion. supportive measures should be applied with particular attention to the maintenance quate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproa dosage. Because naloxone could theoretically also reverse the antiepileptic effects proate, it should be used with caution.

DOSAGE AND ADMINISTRATION

DEPAKOTE tablets and Sprinkle capsules are administered orally. The recommend tial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/da seizures are controlled or side effects preclude further increases. The maximum mended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should b in a divided regimen.

Administration of Sprinkle Capsule: DEPAKOTE Sprinkle capsules may be swa whole or may be administered by carefully opening the capsule and sprinkling the contents on a small amount (teaspoonful) of soft food such as applesauce or puddi drug/food mixture should be swallowed immediately (avoid chewing) and not sto future use. Each capsule is oversized to allow ease of opening.

Conversion from DEPAKENE to DEPAKOTE: In patients previously rec DEPAKENE (valproic acid) therapy, DEPAKOTE products should be initiated same daily dose and dosing schedule. After the patient is stabilized on a DEPA product, a dosing schedule of two or three times a day may be elected in selected pa

DEPAKOTE products provide equal extents of absorption, although they may n duce identical trough and peak valproate concentrations. DEPAKOTE tablets p slightly higher peak concentrations than DEPAKOTE Sprinkle capsules. Such diffe in the maximum and minimum valproate plasma concentrations are unlikely to be of cal significance; however, changes in dosage administration of valproate or conco medications should be accompanied by increased monitoring of plasma concentrati valproate and other medications, as well as the patient's clinical status.

The frequency of adverse effects (particularly elevated liver enzymes) may be related. The benefit of improved seizure control with higher doses should be we against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum concent and therapeutic effect. However, therapeutic valproate serum concentrations for patients will range from 50 to 100 mcg/mL. Some patients may be controlled with or higher serum concentrations (see CLINICAL PHARMACOLOGY)

As the DEPAKOTE dosage is titrated upward, blood concentrations of phenoba and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the with food or by slowly building up the dose from an initial low level.

HOW SUPPLIED

DEPAKOTE Sprinkle capsules (divalproex sodium coated particles in capsules), 12 are white opaque and blue, and are supplied in bottles of 100 (NDC 0074-6114-13 Abbo-Pac® unit dose packages of 100 (NDC 0074-6114-11).

DEPAKOTE tablets (divalproex sodium delayed-release tablets) are supplied as:
125 mg salmon pink-colored tablets:
Bottles of 100 .... (NDC 0074-621
Abbo-Pac® unit dose packages of 100 .... (NDC 0074-6212
250 mg peach-colored tablets:
Bottles of 100 .... (NDC 0074-621
Bottles of 500 .... (NDC 0074-621
Abbo-Pac® unit dose packages of 100 .... (NDC 0074-6214
500 mg lavender-colored tablets:
Bottles of 100 .... (NDC 0074-621
Bottles of 500 .... (NDC 0074-621
Abbo-Pac® unit dose packages of 100 .... (NDC 0074-6215

Recommended Storage: Store tablets below 86°F (30°C).
Store capsules below 77°F (25°C).

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1. Centers for Disease Control, valproate: a new cause of birth defects—report from and follow-up from France. *Morbidity and Mortality Weekly Report.* 1983; 3 438-439
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5. Hurst DL. Expanded therapeutic range of valproate. *Pediatr Neurol* 1987; 3: 342-3

Revised: February, 1992
Caution — Federal (USA) Law prohibits dispensing without prescription.

Stroke
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Today,
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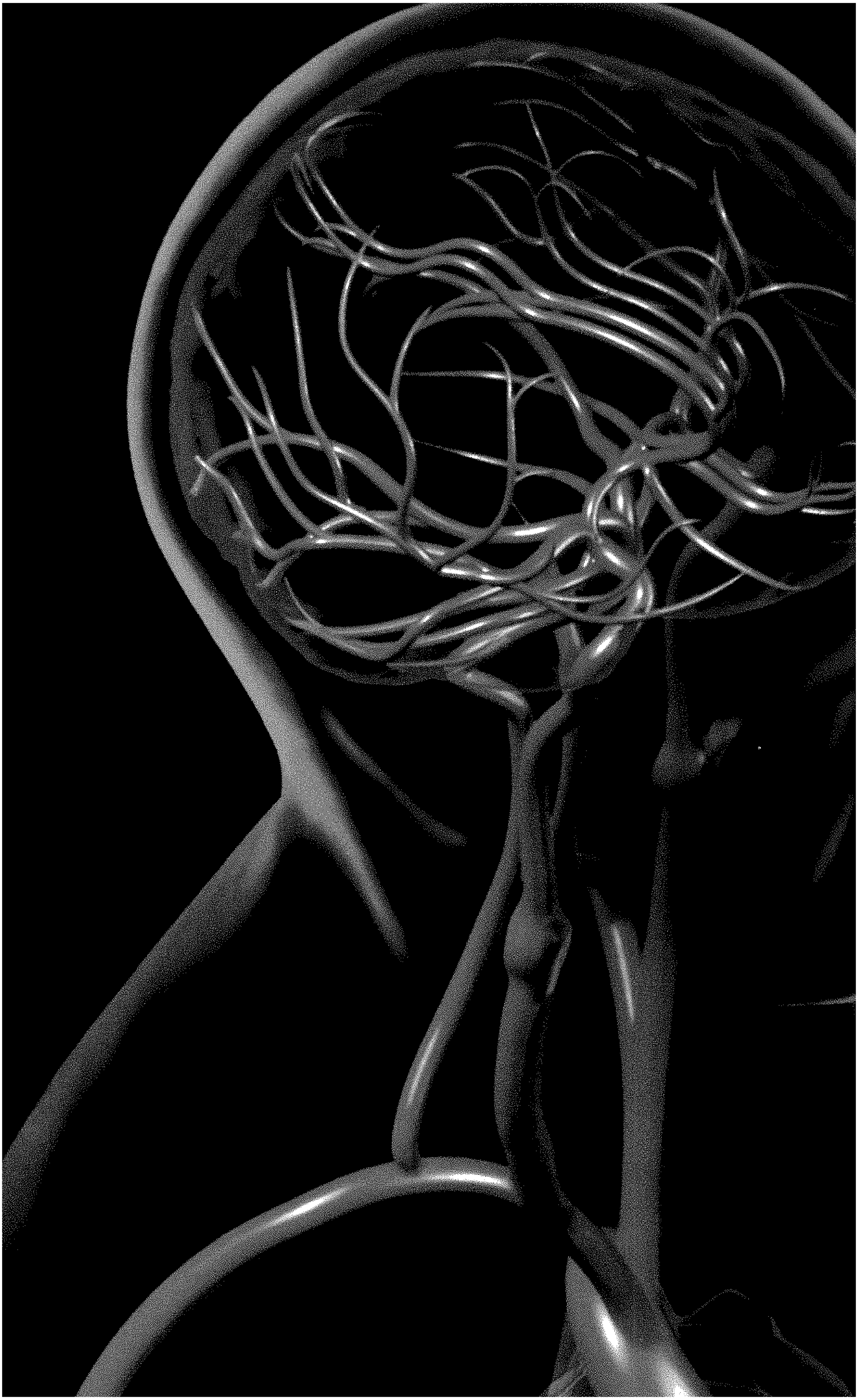

Introducing the First Prescription Antiplatelet Agent that Significantly Reduces the Risk of Stroke[1,2]

Ticlid®

Ticlopidine HCl 250mg Tablets bid

Clinical Trials Demonstrated:

48% reduction vs aspirin[3] in risk of initial stroke in TIA* patients at year 1 (P = .0004, n = 3034), **the year of greatest risk**

33% reduction in risk[2,4] of fatal or nonfatal recurrent stroke at year 1 (P = .008, n = 1053), **the year of greatest risk**

Proven effective in women as well as men[1,2,3,4]

Indications

Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life threatening (see Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke

TICLID, therefore, is appropriate first-line therapy for reducing the risk of thrombotic stroke in:

— all female TIA patients
— all males at risk for recurrent stroke
— all females at risk for recurrent stroke
— all aspirin-intolerant male TIA patients

Side Effects

In clinical trials, neutropenia† occurred in a total of 2.4% of patients (0.8% severe‡) and was not typically associated with clinical signs or symptoms

Therefore, CBC monitoring (including differentials) for neutropenia is essential every 2 weeks for the first 3 months of therapy

The most frequently occurring side effects involved the GI tract: diarrhea (12.5%), nausea (7.0%), dyspepsia (7.0%); rash also occurred (5.1%)

Although most side effects were mild, 21% of patients discontinued therapy due to an adverse event in clinical trials

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*Analysis based on all study participants, which included patients with transient ischemic attack, transient monocular blindness, reversible ischemic neurological deficit, and minor stroke.
†Defined as <1200 neutrophils/mm³, seen in 50/2048 patients.
‡Defined as <450 neutrophils/mm³, seen in 17/2048 patients.

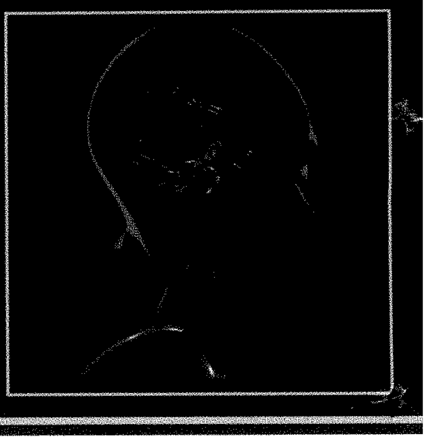
SYNTEX

1. Hass WK, Easton JD, Adams HP Jr et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med.* 1989;321(8):501-507. **2.** Gent M, Easton JD, Hachinski VC et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet.* 1989;1:1215-1220. **3.** TICLID (ticlopidine HCl) tablets full prescribing information. **4.** Biller J, Love BB, Gordon DL. Antithrombotic therapy for ischemic cerebrovascular disease. *Semin Neurol.* 1991;11(4):353-367.

Please see brief summary of prescribing information on last page.

Ticlid®

Ticlopidine HCl 250mg Tablets bid



The First Prescription Antiplatelet Agent that Significantly Reduces the Risk of Stroke

For further information, including the CBC Monitoring Program for TICLID, please call 1-800-TICLID-1.

TICLID® (ticlopidine hydrochloride) 250 mg Tablets

INDICATIONS AND USAGE TICLID is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life-threatening (See Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke. **CONTRAINDICATIONS** The use of TICLID® is contraindicated in the following conditions: Hypersensitivity to the drug. Presence of hematopoietic disorders such as neutropenia and thrombocytopenia. Presence of a hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding). Patients with severe liver impairment.

WARNINGS

Neutropenia

Neutropenia defined in these studies as an ANC <1200 neutrophils/mm^3 occurred in 50 of 2,048 (2.4%) stroke patients who received TICLID in clinical trials. *Severe Neutropenia (<450 neutrophils/mm^3):* Severe neutropenia and/or agranulocytosis occurred in 17 of the 2,048 (0.8%) patients who received TICLID. When the drug was discontinued in these patients, the neutrophil counts returned to normal (>1200 neutrophils/mm^3) within 1-3 weeks. *Mild to Moderate Neutropenia (451-1200 neutrophils/mm^3):* Mild to moderate neutropenia occurred in 33 of the 2,048 (1.6%) patients who received TICLID. Eleven of the patients discontinued treatment and recovered within a few days. In the remaining 22 patients, the neutropenia was transient and did not require discontinuation of therapy. The onset of severe neutropenia occurred 3 weeks to 3 months after the start of therapy with TICLID, with no documented cases of severe neutropenia beyond that time in the large controlled trials. The bone marrow typically showed a reduction in myeloid precursors. It is therefore essential that CBCs and white cell differentials be performed every two weeks starting from the second week to the end of the third month of therapy with TICLID, but more frequent monitoring is necessary for patients whose absolute neutrophil counts have been consistently declining or are 30% less than the baseline count. Neutropenia (an absolute neutrophil count (ANC) of less than 1200 neutrophils/mm^3) is calculated as follows: ANC = WBC × % neutrophils. If clinical evaluation and repeat laboratory testing confirm the presence of neutropenia (<1200/mm^3), the drug should be discontinued. In clinical trials, when therapy was discontinued immediately upon detection of neutropenia, the neutrophil counts returned to normal within 1-3 weeks. After the first three months of therapy, CBCs need be obtained only for patients with signs or symptoms suggestive of infection.

Thrombocytopenia Rarely, thrombocytopenia may occur in isolation or together with neutropenia. If clinical evaluation and repeat laboratory testing confirm the presence of thrombocytopenia (<80,000 cells/mm^3), the drug should be discontinued. Cholesterol Elevation TICLID® therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8-10% within one month of therapy and persist at that level. The ratios of the lipoprotein subfractions are unchanged. **Other Hematological Effects** Rare cases of pancytopenia and thrombotic thrombocytopenic purpura, some of which have been fatal, have been reported in Post-Marketing Surveillance. **Anticoagulant Drugs** The tolerance and safety of coadministration of TICLID with heparin, oral anticoagulants, or fibrinolytic agents has not been established. If a patient is switched from an anticoagulant or fibrinolytic drug to TICLID, the former drug should be discontinued prior to TICLID administration. **PRECAUTIONS General** TICLID should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or pathological conditions. If it is desired to eliminate the antiplatelet effects of TICLID prior to elective surgery, the drug should be discontinued 10-14 days prior to surgery. Several controlled clinical studies have found increased surgical blood loss in patients undergoing surgery during treatment with ticlopidine. In TASS and CATS it was recommended that patients have ticlopidine discontinued prior to elective surgery. Several hundred patients underwent surgery during the trials, and no excessive surgical bleeding was reported. Prolonged bleeding time is normalized within two hours after administration of 20 mg methylprednisolone i.v. Platelet transfusions may also be used to reverse the effect of TICLID on bleeding. **GI Bleeding** TICLID prolongs template bleeding time. The drug should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients on TICLID. (See Contraindications.) **Use in Hepatically Impaired Patients** Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of TICLID is not recommended in this population. (See Clinical Pharmacology and Contraindications.) **Use in Renally Impaired Patients** There is limited experience in patients with renal impairment. In controlled clinical trials, no unexpected problems have been encountered in patients having mild renal impairment and there is no experience with dosage adjustment in patients with greater degrees of renal impairment. Nevertheless, for renally impaired patients it may be necessary to reduce the dosage of ticlopidine or discontinue it altogether, if hemorrhagic or hematopoietic problems are encountered. (See Clinical Pharmacology) **Information for the Patient (See PPI)** Patients should be told that a decrease in the number of white blood cells (neutropenia) can occur with TICLID® especially during the first three months of treatment, and that if neutropenia is severe, it could result in an increased risk of infection. They should be told it is critically important to obtain the scheduled blood tests to detect neutropenia. Patients should also be reminded to contact their physicians if they experience any indication of infection such as fever, chills, and sore throat, all of which may be consequences of neutropenia. All patients should be told that it may take them longer than usual to stop bleeding when they take TICLID and that they should report any unusual bleeding to their physician. Patients should tell physicians and dentists that they are taking TICLID before any surgery is scheduled and before any new drug is prescribed. Patients should be told to report promptly side effects of TICLID such as severe or persistent diarrhea, skin rashes, or subcutaneous bleeding, or any signs of cholestasis, such as yellow skin or sclera, dark urine, or light colored stools. Patients should be told to take TICLID with food or just after eating in order to minimize gastrointestinal discomfort. **Laboratory Tests** *Liver Function:* TICLID therapy has been associated with elevations of alkaline phosphatase and transaminases which generally occurred within 1-4 months of therapy initiation. In controlled clinical trials, the incidence of elevated alkaline phosphatase (greater than 2 times upper limit of normal) was 7.6% in ticlopidine patients, 6.0% in placebo patients and 2.5% in aspirin patients. The incidence of elevated AST (SGOT) (greater than 2 times upper limit of normal) was 3.1% in ticlopidine patients, 4.0% in placebo patients and 2.1% in aspirin patients. No progressive increases were observed in closely monitored clinical trials (e.g. no transaminase greater than 10 times the upper limit of normal was seen), but most patients with these abnormalities had therapy discontinued. Occasionally patients had developed minor elevations in bilirubin. Based on post-marketing and clinical trials experiences, liver function testing should be considered whenever liver dysfunction is suspected, particularly during the first four months of treatment. **Drug Interactions** Therapeutic doses of TICLID caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios, or being given to patients with hepatic impairment, may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine. Studies of specific drug interactions yielded the following results: ***Aspirin:*** Aspirin did not modify the ticlopidine-mediated inhibition of ADP-induced platelet aggregation, but ticlopidine potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of this combination has not been established and concomitant use of aspirin and ticlopidine is not recommended. (See Precautions – GI Bleeding). ***Antacids:*** Administration of TICLID after antacids resulted in an 18% decrease in plasma levels of ticlopidine. ***Cimetidine:*** Chronic administration of cimetidine reduced the clearance of a single dose of TICLID by 50%. ***Digoxin:*** Co-administration of TICLID with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected. ***Theophylline:*** In normal volunteers, concomitant administration of TICLID resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hr and a comparable reduction in total plasma clearance of theophylline. ***Phenobarbital:*** In six normal volunteers, the inhibitory effects of TICLID on platelet aggregation were not altered by chronic administration of phenobarbital. ***Phenytoin:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID and it may be useful to remeasure phenytoin blood concentrations. ***Propranolol:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID.

℞ ____________

TICLID 250 mg
#30
Sig: 1 Tab bid
with meals

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, TICLID was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs without evidence of clinically significant adverse interactions. (See Precautions.) **Food Interaction:** The oral bioavailability of ticlopidine is increased by 20% when taken after a meal. Administration of TICLID with food is recommended to maximize gastrointestinal tolerance. In controlled trials, TICLID was taken with meals. **Carcinogenesis, Mutagenesis, Impairment of Fertility** In a two-year oral carcinogenicity study in rats, ticlopidine at daily doses of up to 100 mg/kg (610 mg/m^2) was not tumorigenic. For a 70 kg person (1.73m^2 body surface area), the dose represents 14 times the recommended clinical dose on a mg/kg basis and 2 times the clinical dose on body surface area basis. In a 78 week oral carcinogenicity study in mice ticlopidine at daily doses up to 275 mg/kg (1180 mg/m^2) was not tumorigenic. The dose represents 40 times the recommended clinical dose on a mg/kg basis and 4 times the clinical dose on body surface area basis. Ticlopidine was not mutagenic in *in vitro* Ames test, rat hepatocyte DNA-repair assay, and Chinese hamster fibroblast chromosomal aberration test and *in vivo* mouse spermatozoid morphology test, Chinese hamster micronucleus test and Chinese hamster bone marrow cell sister chromatid exchange test. Ticlopidine was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day. **Pregnancy: Teratogenic Effects** Pregnancy Category B. Teratology studies have been conducted in mice (doses up to 200 mg/kg/day), rats (doses up to 400 mg/kg/day) and rabbits (doses up to 200 mg/kg/day). Doses of 400 mg/kg in rats, 200 mg/kg/day in mice, and 100 mg/kg in rabbits produced maternal toxicity as well as fetal toxicity, but there was no evidence of a teratogenic potential of ticlopidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers** Studies in rats have shown ticlopidine is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ticlopidine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** Safety and efficacy in patients under the age of 18 have not been established. **Geriatric Use** Clearance of ticlopidine is somewhat lower in elderly patients and trough levels are increased. The major clinical trials with TICLID were conducted in an elderly population with an average age of 64 years. Of the total number of patients in the therapeutic trials, 45% of patients were over 65 years old and 12% were over 75 years old. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse reactions were relatively frequent, with over 50% of patients reporting at least one. Most (30 to 40%) involved the gastrointestinal tract. Most adverse effects are mild, but 21% of patients discontinued therapy because of an adverse event, principally diarrhea, rash, nausea, vomiting, G.I. pain, and neutropenia. Most adverse effects occur early in the course of treatment, but a new onset of adverse effects can occur after several months. The incidence rates of adverse events listed in the following table were derived from multicenter, controlled clinical trials described above comparing TICLID, placebo, and aspirin over study periods of up to 5.8 years. Adverse events considered by the investigator to be probably drug-related that occurred in at least one percent of patients treated with TICLID are shown in the following table:

Percent of Patients with Adverse Events in Controlled Studies

Event	TICLID (n = 2048) Incidence	Aspirin (n = 1527) Incidence	Placebo (n = 536) Incidence
Any Events	*60.0 (20.9)*	*53.2 (14.5)*	*34.3 (6.1)*
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	1.7 (0.9)
Dyspepsia	7.0 (1.1)	9.0 (2.0)	0.9 (0.2)
Rash	5.1 (3.4)	1.5 (0.8)	0.6 (0.9)
GI Pain	3.7 (1.9)	5.6 (2.7)	1.3 (0.4)
Neutropenia	2.4 (1.3)	0.8 (0.1)	1.1 (0.4)
Purpura	2.2 (0.2)	1.6 (0.1)	0.0 (0.0)
Vomiting	1.9 (1.4)	1.4 (0.9)	0.9 (0.4)
Flatulence	1.5 (0.1)	1.4 (0.3)	0.0 (0.0)
Pruritus	1.3 (0.8)	0.3 (0.1)	0.0 (0.0)
Dizziness	1.1 (0.4)	0.5 (0.4)	0.0 (0.0)
Anorexia	1.0 (0.4)	0.5 (0.3)	0.0 (0.0)
Abnormal Liver Function test	1.0 (0.7)	0.3 (0.3)	0.0 (0.0)

Incidence of discontinuation, regardless of relationship therapy, is shown in parentheses.

Neutropenia/Thrombocytopenia See Warnings. **Gastrointestinal** TICLID therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and typically are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. **Hemorrhagic** TICLID has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding and perioperative bleeding. Intracerebral bleeding was rare in clinical trials with TICLID, with an incidence no greater than that seen with comparator agents. (Ticlopidine 0.5%, aspirin 0.6%, placebo 0.75%.) **Rash** Ticlopidine has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean onset time of 11 days. If drug is discontinued, recovery occurs within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of severe rashes. **Less Frequent Adverse Reactions (Probably Related)** Clinical adverse experiences occurring in 0.5 to 1.0 percent of patients in the controlled trials include: Digestive System: GI fullness. Skin and Appendages: urticaria. Nervous System: headache. Body as a Whole: asthenia, pain. Hemostatic System: epistaxis. Special Senses: tinnitus. In addition, rarer, relatively serious events have also been reported, mainly from foreign post marketing experience: Pancytopenia, hemolytic anemia with reticulocytosis, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, cholestatic jaundice, nephrotic syndrome, myositis, hyponatremia, immune thrombocytopenia and thrombocytopenic thrombotic purpura (TTP). **OVERDOSAGE** One case of deliberate overdosage with TICLID has been reported by foreign postmarketing surveillance program. A 38 year old male took a single 6000 mg dose of TICLID (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Single oral doses of ticlopidine at 1600 mg/kg and 500 mg/kg were lethal to rats and mice, respectively. Symptoms of acute toxicity were GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and abnormal gait. **DOSAGE AND ADMINISTRATION** The recommended dose of TICLID is 250 mg BID taken with food. Other doses have not been studied in controlled trials for these indications.

SYNTEX
SYNTEX LABORATORIES, INC.
PALO ALTO, CA 94304

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Vitamin B_{12} Metabolism in Multiple Sclerosis

E. H. Reynolds, FRCP; T. Bottiglieri, MSc, PhD; M. Laundy, HNC; R. F. Crellin, MRCP; S. G. Kirker, MRCP(Ire)

• We have previously described 10 patients with multiple sclerosis (MS) and unusual vitamin B_{12} deficiency. We have therefore studied vitamin B_{12} metabolism in 29 consecutive cases of MS, 17 neurological controls, and 31 normal subjects. Patients with MS had significantly lower serum vitamin B_{12} levels and significantly higher unsaturated R-binder capacities than neurological and normal controls, and they were significantly macrocytic compared with normal controls. Nine patients with MS had serum vitamin B_{12} levels less than 147 pmol/L and, in the absence of anemia, this subgroup was significantly macrocytic and had significantly lower red blood cell folate levels than neurological and normal controls. Nine patients with MS had raised plasma unsaturated R-binder capacities, including three patients with very high values. There is a significant association between MS and disturbed vitamin B_{12} metabolism. Vitamin B_{12} deficiency should always be looked for in patients with MS. The cause of the vitamin B_{12} disorder and the nature of the overlap with MS deserve further investigation. Coexisting vitamin B_{12} deficiency might aggravate MS or impair recovery from MS.

(*Arch Neurol.* 1992;49:649-652)

After describing three patients with multiple sclerosis (MS) and unusual vitamin B_{12} deficiencies,[1,2] seven further examples were referred in 1 year to one of us (E.H.R.) by other neurologists.[3-5] The nature of the relationship between the demyelinating disorder and the vitamin B_{12} deficiency was uncertain, and this prompted us to study vitamin B_{12} metabolism in unselected populations of patients with MS. In a retrospective survey of admissions to King's College Hospital, London, England, in 1988, we confirmed an old but forgotten observation that patients with MS may be mildly macrocytic.[6] The cause of the macrocytosis was uncertain, especially as vitamin B_{12} and folate assays were not routinely undertaken. We now report a prospective study of vitamin B_{12} metabolism in an unselected series of patients who were attending King's College Hospital.

PATIENTS AND METHODS

The 29 consecutive patients with MS were attending the neurological outpatient department at King's College Hospital. There were 23 females and six males, with a mean age of 43 years (age range, 22 to 67 years). All patients had a diagnosis of definite MS that had been established on the basis of clinical evidence of multiple fluctuating lesions in the nervous system, supported by neurophysiological or magnetic resonance imaging data and the detection of oligoclonal bands in the cerebrospinal fluid (CSF). Patients who were taking steroid or immunosuppressant therapy or vitamin B_{12} were not included. Patients who were referred to our clinic from other centers because of our interest in MS and vitamin B_{12} deficiency were not included. One patient with MS was 8 months' pregnant, and another patient was taking folic acid. The median duration of the disorder from the first symptom was 6.5 years (duration range, 0.1 to 32 years).

Eighteen normal control subjects were drawn from the staff of King's College Hospital and Northwick Park Hospital, London, England. There were eight females and 10 males, with a mean age of 33.8 years (age range, 26 to 54 years). An additional 13 normal control subjects (eight females and five males, with a mean age of 35.8 years [age range, 27 to 58 years]) had vitamin B_{12}–binder data only collected. Seventeen neurological control subjects were drawn from the neurological department at King's College Hospital. There were 10 females and seven males, with a mean age of 55 years (age range, 20 to 77 years). Patients with dementia, depression, or subacute combined degeneration were not included. Nine patients had back or root pain, degenerative disk disease with or without root or spinal cord compression, four had sleep disorders, two had motor neuron disease, one had viral meningitis, and one had headaches.

Hemoglobin values and mean cell volumes (MCVs) were measured on a Coulter S counter. Serum vitamin B_{12} levels were determined by an isotope dilution assay that used polyacrylamide-bound intrinsic factor to bind cyanocobalamin labeled with Cobalt 57 and endogenous vitamin B_{12} in serum.[7] Samples for assay of unsaturated vitamin B_{12} binders were collected in tubes that contained 2 mg of sodium fluoride and 1 mg of disodium–ethylenediaminetetraacetic acid (EDTA) for each 1.0 mL of blood, and plasma was removed within 1 hour of collection. Samples that are obtained in this way prevent artifactual release of R binder from leukocytes. Plasma unsaturated transcobalamin II (TCII) and unsaturated R-binder capacity were measured by saturating the binding proteins with ^{57}Co cyanocobalamin and then separating the proteins by gel chromatography.[8] Red blood cell folate was assayed with *Lactobacillus casei.*

Statistical Analysis

Values for serum vitamin B_{12}, TCII, R-binder capacity, and red blood cell folate were not normally distributed, and these data were logarithmically transformed for statistical analysis. The hematological and biochemical data in the MS and two control

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Hemoglobin, MCV, Serum Vitamin B_{12}, Unsaturated TCII and R-Binder Capacity, and Red Cell Folate in Normal Controls, Neurological Controls, and Patients With Multiple Sclerosis*

	Normal Controls (N=18)		Neurological Controls (N=17)		Multiple Sclerosis (N=29)	
	Mean±SE	Antilog Mean (95% Confidence Interval)	Mean±SE	Antilog Mean (95% Confidence Interval)	Mean±SE	Antilog Mean (95% Confidence Interval)
Hemoglobin, g/L	139±30	. . .	130±30	. . .	134±30	. . .
MCV, fL	90.9±1.3	. . .	91.7±1.4	. . .	94.0±1.1†‡§	. . .
Serum vitamin B_{12}, pmol/L	253±18	241 (207;282)	275±26	258 (213;313)	194±15	177 (148;210)‖¶#
TCII, pmol/L	736±21**	726 (681;774)	677±47	658 (563;771)	730±47	686 (590;797)
R-binder capacity, pmol/L	64±5**	59 (50;68)	62±7	58 (22;75)	202±64	110 (74;162)††‡‡§§
Red cell folate, nmol/L	819±93	749 (606;921)	898±54	871 (769;991)	735±88	677 (527;801)

*MCV indicates mean cell volume; TCII, transcobalamin II. Analysis of variance for serum vitamin B_{12} was F=6.08; $P<.004$; for R-binder capacity, F=7.08; $P<.002$.

†*t* test vs normal controls: $t=2.07$; $P<.05$.

‡*t* test vs neurological controls: $t=1.33$; $P=.19$ (not significant).

§*t* test vs combined controls: $t=1.99$; $P<.05$.

‖*t* test vs normal controls: $t=2.81$; $P<.01$.

¶*t* test vs neurological controls: $t=3.06$; $P<.005$.

#*t* test vs combined controls: $t=3.38$; $P<.002$.

**N=31 (includes 13 subjects with binder data only).

††*t* test vs normal controls: $t=3.09$; $P<.005$.

‡‡*t* test vs neurological controls: $t=2.87$; $P<.01$.

§§*t* test vs combined controls: $t=3.17$; $P<.004$.

groups were compared by *t* test and by analysis of variance (Table). Correlations were examined with the use of Spearman Rank Correlation Coefficients.

RESULTS

Hemoglobin

There were no significant differences among the three groups. Two patients with MS had slightly low hemoglobin values (106 and 107 g/L, respectively). Although both patients had serum vitamin B_{12} levels below 147 pmol/L (140 and 103 pmol/L, respectively), both patients also had a history of iron deficiency, and one had the lowest MCV in the MS series (ie, 82.2 fL). The other patient had an MCV of 91.3 fL.

Mean Cell Volume

The MCV was significantly elevated in the MS group compared with that in the normal control group and the combined control groups, but it was just short of significance compared with that in the neurological control group alone. Nine patients with MS had an MCV greater than 95 fL, whereas this occurred in only two normal controls and three neurological controls.

Serum Vitamin B_{12}

This value was significantly lower in the MS group (Fig 1). Nine patients with MS had serum vitamin B_{12} values below 147 pmol/L (ie, 200 pg/mL), but this occurred in only one normal control and one neurological control.

Transcobalamin II

There were no significant differences among the three groups. Three patients with MS had slightly low values (352, 328, and 265 pmol/L, respectively; normal control range, 481 to 885pmol/L; and neurological control range, 477 to 928 pmol/L).

R-Binder Capacity

This value was significantly elevated in the MS group compared with that in both control groups (Fig 2). Nine patients with MS had values greater than the highest control level of 133 pmol/L, including three patients with extremely high values of 1476, 860, and 690 pmol/L, respectively.

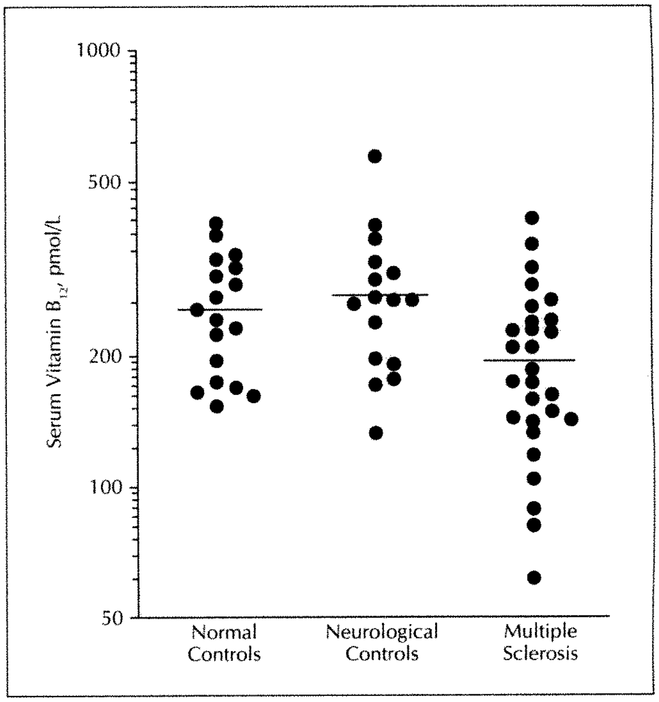

Fig 1.—*Serum vitamin B_{12} values in normal controls, neurological controls, and patients with multiple sclerosis. Log scale.*

Red Blood Cell Folate

The patient who was taking folic acid was excluded from this analysis. There were no significant differences among the three groups, but two patients with MS had values below 339 nmol/L (312 and 201 nmol/L, respectively). One of these patients also had a low serum vitamin B_{12} value (88 pmol/L) and a high MCV (104 fL) but was not anemic.

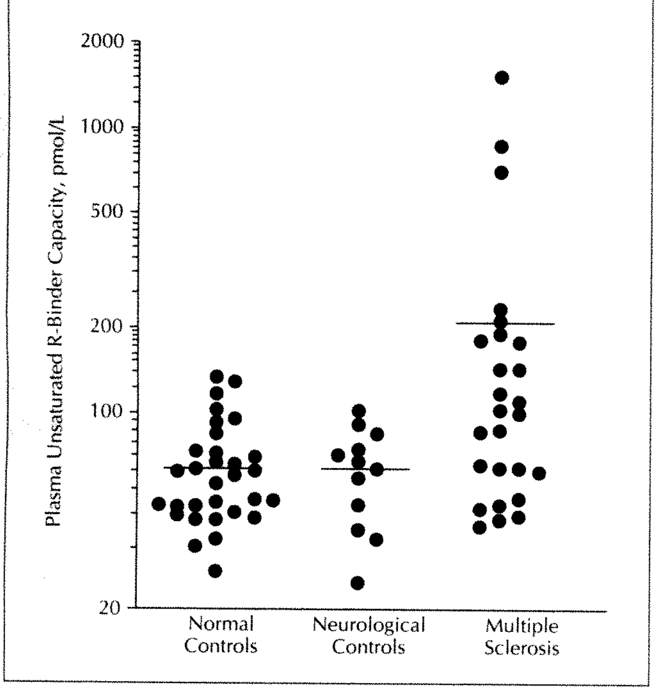

Fig 2.—*Unsaturated plasma R-binder capacity values in normal controls, neurological controls, and patients with multiple sclerosis. Log scale.*

A correlation analysis showed no significant relations among values for MCV, serum vitamin B_{12}, TCII, R binder, and red blood cell folate in control groups or patients with MS (even after exclusion of three patients with MS with very high unsaturated R-binder capacities), with the single exception of a positive correlation between serum vitamin B_{12} and R-binder values in control subjects ($r = .86$, $P < .001$). There were no correlations among any of the metabolic variables and the age or duration of symptoms in patients with MS.

After excluding the two patients with anemia, the subgroup of patients with MS and vitamin B_{12} levels below 147 pmol/L were significantly macrocytic (MCV, 96.0±1.5 fL[mean±SE]) compared with normal controls (MCV, 90.9±1.3 fL; $t = 2.84$, $P < .02$) and neurological controls (MCV, 91.7±1.4 fL; $t = 2.17$, $P < .05$), and they had significantly lower red blood cell folate values [mean±SE] (489±86 nmol/L) compared with that in normal controls (820±92 nmol/L; $t = 2.54$, $P < .05$) and neurological controls (899±54 nmol/L; $t = 3.58$, $P < .01$). Although the R-binder capacity was higher in this subgroup (282±200 pmol/L), the differences between normal controls (64±5 pmol/L) and neurological controls (62±7 pmol/L) were not significant.

COMMENT

In a consecutive series of patients with MS, we have found significantly lower serum vitamin B_{12} levels, including nine patients with levels below 147 pmol/L (ie, 200 pg/mL). We have used the level of 147 pmol/L as a cutoff point, as Lindenbaum et al[9] have shown that neurological disease can occur at and below this level and occasionally even above it. We agree with Lindenbaum et al[9] that such patients, although not anemic, were probably truly vitamin B_{12} deficient because they were significantly macrocytic, had significantly lower red blood cell folate values, as is known to occur in vitamin B_{12} deficiency,[10] and also had raised plasma homocysteine levels (T.B., PhD thesis submitted to London University, 1992). Between 1957 and 1965, there were several studies of serum vitamin B_{12} in MS,[11-17] because of interest in a possible role for vitamin B_{12} in myelin formation. Some of the earlier studies reported that serum vitamin B_{12} levels were low,[11,12,14] but some later studies were "negative."[13,15-17] It is interesting in retrospect that six of the 46 patients who were described by Simpson[16] clearly had low serum vitamin B_{12} levels (range, 47 to 87 pmol/L); this finding was not seen in the control group. Early reports,[14-17] between 1962 and 1965, of CSF vitamin B_{12} levels in MS were also conflicting, although there was a tendency for mean CSF vitamin B_{12} levels to be lower. We have not measured the CSF vitamin B_{12} level in this study as a sensitive enough assay to detect differences in the low concentrations of vitamin B_{12} that are normally present in CSF was not available. With the use of a new and more sensitive technique, however, Nijst et al[18] have recently reported that CSF vitamin B_{12} levels are significantly lower in MS. Furthermore, there was a trend toward lower serum vitamin B_{12} levels, as well as a significant correlation between serum and CSF vitamin B_{12} levels in MS.

In our previously reported series of 10 patients with MS and vitamin B_{12} deficiency, we were unable to explain the cause of the deficiency, with only two or possibly three of them having pernicious anemia (PA).[4,5] We suspected a disturbance of vitamin B_{12} binding or transport and have therefore included unsaturated R-binder and TCII assays in this study. We found no significant abnormalities of TCII in MS, although three patients had slightly low values. However, we have found a significant elevation in the unsaturated R-binder capacity, including three patients with very high values (Fig 2). The unsaturated R-binder capacity was highly correlated with the serum vitamin B_{12} level in our control subjects but not in the patients with MS. The function of R-binder is unknown, although a role in removing toxic cobalamins from the brain has been postulated.[19] There are three cases in the literature of a possible association between MS and R-binder deficiency.[20,21] To our knowledge, there are no reports of neurological disease associated with excess R binder.

The mild degree of macrocytosis in our patients with MS is similar to that observed in our retrospective study.[6] This finding has also recently been confirmed in a series of patients with newly diagnosed MS,[22] supporting our view that it is not the result of the disease or its treatment. We do not know yet whether the abnormalities of serum vitamin B_{12} or R binder are responsible for the mild macrocytosis in MS. The correlations between values for MCV and serum vitamin B_{12}, and between values for MCV and R binder, were weak. There are other causes of macrocytosis, such as folate deficiency, and two of our patients had low red blood cell folate levels. None of our patients were alcoholic, and we excluded patients who were taking immunosuppressive drugs. Only two of our patients were slightly anemic, and although both had low serum vitamin B_{12} levels, the anemia was probably at least in part due to iron deficiency. Iron deficiency is a significant association of vitamin B_{12} deficiency, especially PA.[10]

The cause of low serum vitamin B_{12} levels and high unsaturated R-binder capacities in some of our patients is uncertain. As in our original series of 10 cases,[4,5] it was possible that some, but unlikely that all, had PA. Lauer and Firnhaber[23] found borderline or definitely abnormal vitamin B_{12} absorption (without intrinsic factor) in 27% of 74 patients with MS. Serum vitamin B_{12} levels were not included in the latter study.

Much is known about the epidemiology of MS, but for vitamin B_{12} deficiency, epidemiological data are only available for PA. An important point is that MS is a disorder of young people; PA is a disorder of middle and late life. Less than 10% of patients with PA present before the age of 40 years.[10] The risk of MS and PA or other vitamin B_{12} deficiencies occurring together by chance (in the MS age range) is remote.[5] It is, however, remarkable that despite the fact that the age range is so different, the sex, racial, and geographical distribution of PA and MS are similar.[5,6] Thus, PA has a higher prevalence in northern Europe compared with that in southern Europe and tropical areas, a diminishing prevalence from the north to the south in the United Kingdom, and a higher incidence in white than black North Americans.[6,10] The female-male ratio in both disorders is 1.3:1. Najim Al-Din et al[22] have also drawn attention to some similarities in the HLA associations of MS and PA, particularly with respect to HLA-A3, HLA-B7, HLA-DRw2, and HLA-DR2.

Our observations suggest that there is a significant association between MS and vitamin B_{12} deficiency and that vitamin B_{12} deficiency should always be looked for in MS. The nature and significance of the overlap of the two disorders, however, requires clarification. The similarity in epidemiology and possible HLA associations of MS and PA may suggest a linked pattern of genetic predisposition to the two disorders. Another possible interpretation is that the vitamin B_{12} deficiency, from whatever cause, renders some patients more vulnerable to the putative viral/immunological mechanisms that are widely suspected in MS.[4,5] There is some evidence that isolated vitamin deficiencies, including deficiency of vitamin B_{12}, can impair immunological processes.[24] A further possibility is that chronic immune reactions or recurrent central nervous system repair processes increase the demand for vitamin B_{12}. It is difficult to see how a deficiency that usually leads to various well-known progressive neurological syndromes should also cause a previously unrecognized relapsing and remitting syndrome. However, the question may be asked when MS and vitamin B_{12} deficiency coexist, as they clearly do in at least some patients, whether the vitamin deficiency is aggravating the underlying demyelinating disorder or impairing recovery? The fact is that for some 30 years there has been a vogue for treating MS with injections of vitamin B_{12}. Although this is done for placebo purposes, this was not the original intention, and furthermore, some patients are impressed with their neurological benefit. We are unaware of any evidence or claims that vitamin B_{12} treatment might aggravate MS. If there is, as we suspect in some patients with MS, a disorder of vitamin B_{12} binding or transport, questions arise about the form, dose, and frequency of vitamin B_{12} treatment that might be appropriate. Little is known about the transport of vitamin B_{12} into, and the requirements of the nervous system for, vitamin B_{12}.[25] What may be suitable for hematological purposes may not necessarily be appropriate for neurological improvement.[26] Clearly, further treatment studies are now indicated with the use of modern monitoring techniques and distinguishing patients with and without evidence of vitamin B_{12} deficiency.

In conclusion, the association of MS and a disturbance of vitamin B_{12} metabolism that we have found in some patients opens up an interesting new lead in the search for an understanding of this neurological disorder.[2]

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Original Contribution

The Role of Hypotension in Septic Encephalopathy Following Surgical Procedures

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• To study the risk factors for septic encephalopathy, we reviewed a consecutive series of 84 patients with septic syndrome and multiple-organ failure. Septic encephalopathy developed in 14 of these patients. Univariate analysis revealed that severe hypotension was significantly associated with the development of septic encephalopathy. In stepwise multiple logistic regression analysis, no other variable made a significant contribution in the presence of severe cardiovascular failure. Septic encephalopathy may be related to ischemic damage rather than to metabolic causes.

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The term septic encephalopathy has been introduced to describe a form of encephalopathy in which critically ill patients with sepsis manifest a clouding of consciousness that may be associated with transient focal signs, seizures, or myoclonus.[1] It has recently become evident that the majority of the patients with this neurological complication die.[2,3]

The nature of septic encephalopathy remains elusive. Of many metabolic variables that have been considered in septic syndrome and multiple-organ failure, none have correlated closely with the development of this encephalopathy.[3] One report has suggested that amino acid derangements are directly involved[4]; other authors have tentatively ascribed it in some patients to primary microabscess formation based on findings from postmortem examinations.[1]

A major drawback, however, in these earlier studies was the lack of a Sepsis Severity Scoring system and of a comparison of the degree of multiple-organ failure with the clinical presentation of septic encephalopathy. Hypotension develops in approximately half of the patients with septic syndrome, and these patients may need vasopressors. The purpose of this investigation was to evaluate the possibility that septic encephalopathy is, at least, partly hypoxic-ischemic in origin.

METHODS

We reviewed a consecutive series of 84 patients with sepsis following recent thoracic and abdominal surgery; these patients had been admitted to the Surgical Intensive Care Unit, University Hospital, Utrecht, the Netherlands, from August 1989 to April 1991. Patients with a history of multiple trauma or evidence of central nervous system disease were excluded. To diagnose a clinical suspicion of sepsis, at least four of the following clinical criteria should be present[5]: (1) fever (temperature, >39°C) or hypothermia (temperature, <35°C); (2) tachypnea (respirations, >28/min); (3) tachycardia (pulse rate, >100 beats per minute); (4) systolic blood pressure, less than 90 mm/Hg; (5) abnormal white blood cell count ($<3.5 \times 10^9$/L or $>15.0 \times 10^9$/L), abnormal neutrophil count (<0.35 or >0.85 of the total white blood cell count), or abnormal immature neutrophil count (>0.20 of the total white blood cell count); (6) thrombocytopenia (platelet count, $<100 \times 10^9$/L); and (7) presence of an obvious primary septic site.

All patients with clinical evidence of a septic encephalopathy were seen by one of us (E.F.M.W.). Patients with a presumed septic encephalopathy met the following criteria—a decreased level of consciousness with at least one of the following signs: (1) focal or generalized seizures, (2) multifocal myoclonus, and (3) hemiparesis and/or gaze palsy. When patients were treated with sedatives, a second neurological evaluation of the patients was performed after discontinuation of these drugs.

The patient charts and available computed tomographic scans were reviewed, and the data were compiled and analyzed. To define the severity of surgical infection, we used the most pertinent elements of the Severity Sepsis Score, as devised by Stevens[6] and Skau and colleagues.[7] The possible range of scores under this system is given in the following enumeration:

1. Lung: no intervention, score of 0; oxygen by mask, score of 1; intubated (no positive end-expiratory pressure), score of 2; positive end-expiratory pressure (range, 0 to 10 cm H_2O), score of 3; positive end-expiratory pressure (>10 cm H_2O) and Po_2 (>50 mm Hg), score of 4; and Po_2 (<50 mm Hg) and positive end-expiratory pressure (>10 cm H_2O), score of 5.
2. Kidney: creatinine level (<133 µmol/L), score of 0; creatinine level (range, 133 to 221 µmol/L), score of 1; creatinine level (range, 230 to 318 µmol/L), score of 2; creatinine level (>318 µmol/L) and adequate urine volume, score of 3; creatinine level (>318 µmol/L) and urine volume (range, 20 to 50 mL/h), score of 4; and creatinine level (>318 µmol/L) and urine volume (≤20 mL/h), score of 5.
3. Cardiovascular: mean arterial blood pressure (>75 mm Hg), score of 0; mean arterial blood pressure (range, 75 to 70 mm Hg), score of 1; mean arterial blood pressure (<70 mm Hg), score of 2; mean arterial blood pressure (>75 mm Hg with dopamine hydrochloride treatment [<5 µg/kg per minute]), score of 3; mean

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arterial blood pressure (>75 mm Hg with dopamine hydrochloride treatment [>5 μg/kg per minute]), score of 4; and mean arterial blood pressure (range, 70 to 60 mm Hg despite dopamine treatment), score of 5.

4. Liver: normal lactate dehydrogenase, alanine and aspartate aminotransferase, and bilirubin levels, score of 0; increased lactate dehydrogenase and alanine and aspartate aminotransferase levels and normal bilirubin level, score of 1; bilirubin level range of 26 to 43 μmol/L, score of 2; bilirubin level range of 44 to 68 μmol/L, score of 3; bilirubin level range of 70 to 145 μmol/L, score of 4; and a precoma bilirubin level greater than 145 μmol/L.

In a univariate analysis, the relationship between clinical and laboratory variables and the presence of septic encephalopathy was studied with the use of the χ^2 test. Variables that were significantly related to septic encephalopathy were entered into a logistic regression model to determine the independent relationship of the selected variables with septic encephalopathy. For each of the organ systems, we defined severe organ failure as a Sepsis Severity Score of 3 or higher.

RESULTS

The patients' ages ranged from 36 to 80 years (mean age, 66 years). Thirty-six patients (43%) were male.

Fourteen patients fulfilled the clinical criteria for septic encephalopathy. All 14 patients had a depressed level of consciousness beyond drowsiness, and half of the patients were unresponsive to pain. Focal or generalized seizures were noted in six patients. Myoclonic jerks were relatively infrequent and present in only six of 14 patients. Hemiparesis that shifted from side to side was noted in two patients. Cerebrospinal fluid samples that were obtained in five of 14 patients with septic encephalopathy were normal.

No abnormalities were noted on computed tomographic scans that were available for review in seven patients. Neuropathological examinations that were performed in two patients with septic encephalopathy revealed widespread ischemic damage in the cerebral cortex. No microabscesses were identified.

The clinical characteristics are tabulated in the Table. Fever (temperature, >39°C) and chest infections were significantly more common in patients with septic encephalopathy (Table). There was a trend for more physiological abnormalities in patients with septic encephalopathy, but none of the differences reached statistical significance. The failure of specific organ systems, as related to the development of septic encephalopathy, is illustrated in the Figure.

A univariate association with septic encephalopathy was found with severe cardiovascular failure ($P<.01$). There were no significant associations with severe renal failure ($P=.23$), severe hepatic failure ($P=.79$), and severe respiratory failure ($P=.41$).

Stepwise multiple logistic regression of variables that were considered in the univariate analysis indicated that cardiovascular failure was the most powerful predictor of septic encephalopathy ($P<.01$). No other variable made a significant contribution in the presence of this variable.

Mortality in patients whose conditions were complicated with septic encephalopathy was higher than the mortality in patients without clinical evidence of septic encephalopathy (79% [11/14] vs 51% [36/70]). Three patients with septic encephalopathy with drowsiness and generalized seizures recovered, but cognitive functions were not assessed.

Univariate Analysis of Clinical Characteristics of Sepsis With SE*

	No. (%) of Patients		
Characteristic	SE (n=14)	NSE (n=70)	*P*
Temperature, >39°C	10 (71)	10 (14)	<.01
Chest infection	10 (71)	19 (27)	<.01
Wound infection	2 (14)	9 (13)	NS
Cardiovascular failure (SSS, ≥3)	11 (79)	27 (39)	<.01
Renal failure (SSS, ≥3)	10 (71)	30 (43)	NS
Hepatic failure (SSS, ≥3)	6 (42)	28 (40)	NS
Respiratory failure (SSS, ≥3)	10 (71)	37 (53)	NS
Ileus	4 (29)	18 (26)	NS
Gram-positive blood culture	5 (36)	26 (37)	NS
Gram-negative blood culture	2 (14)	5 (7)	NS
Mixed blood culture	4 (29)	12 (17)	NS
Plasma albumin level (<30 g/L)	9 (64)	26 (37)	NS
Hemoglobin level (<70 g/L)	11 (79)	53 (76)	NS
Leukocyte count (>30×10^9/L)	1 (7)	13 (13)	NS
Platelet count (<100×10^9/L)	8 (57)	28 (40)	NS
Compensated metabolic acidosis	1 (7)	14 (20)	NS
Uncompensated metabolic acidosis	6 (43)	23 (33)	NS

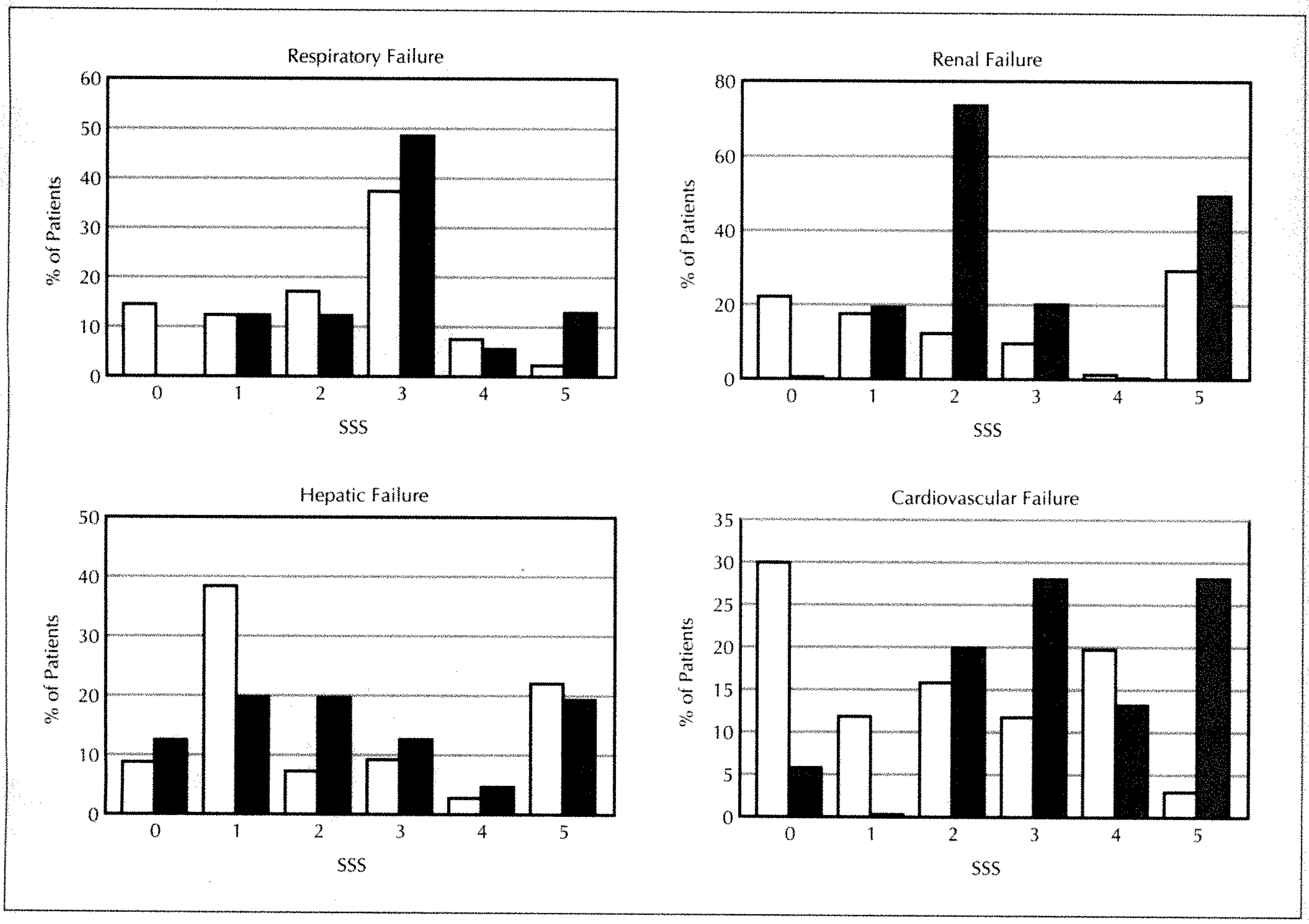
*SE indicates septic encephalopathy; NSE, no evidence of septic encephalopathy; NS, not significant; and SSS, Sepsis Severity Score.

COMMENT

Septic encephalopathy usually occurs in the intensive care unit setting, and failure to awaken following a septic episode is a frequently encountered problem of neurologists who provide consultative services. An important purpose of our research was to define factors that make a critical contribution to the development of septic encephalopathy. Septic encephalopathy refers to a clinical syndrome that probably represents one of the diffuse and metabolic brain disorders. The syndrome is characterized by a decrease in the level of consciousness that may progress to complete unresponsiveness, fluctuating focal signs, seizures, and myoclonic jerks. Our study showed that most patients had a decreased level of consciousness as the cardinal feature of septic encephalopathy and focal signs, myoclonus, or any constellation of symptons were rare. These clinical features bear resemblance to anoxic-ischemic or any other form of metabolic encephalopathy, and therefore, the term septic encephalopathy has not gained universal acceptance and credibility.

The chief finding of the present study is that patients with hypotension who were treated with increasing doses of vasopressors in the surgical intensive care unit were at risk for encephalopathy. Multiple-organ system failure is common in septic shock, but the contribution of other elements of organ failure was not prominent in our series of patients and, in particular, did not complement the significant association of hypotension with septic encephalopathy. This suggests that in septic encephalopathy, the impact of prolonged episodes of hypotension may be greater than that of metabolic abnormalities.

Some caution is in order in interpreting the results. The



Correlation of the severity of organ failure and incidence of septic encephalopathy. SSS indicates Sepsis Severity Score (see "Methods" section for description); open bars, no evidence of septic encephalopathy; and closed bars, evidence of septic encephalopathy.

retrospective design of this study and the relatively small number of patients with septic encephalopathy prevent the conclusions from being more than suggestive. Only patients with neurological signs alerted the surgeon to consult the neurologist, and other patients with sepsis may have been heavily sedated which could have prevented the detection of clinical neurological signs. Moreover, the conditions of our patients, in whom many had multiple-organ failure, may have represented the most severe end of the disease spectrum. However, if we accept these limitations, our results may shed some light on the mechanism that produces septic encephalopathy. Little information is presently available on the potential causes of septic encephalopathy. On the basis of neuropathological evidence of disseminated microabscesses in eight of 14 consecutive patients, one provocative study raised the possibility that bacterial inoculation in the brain may be involved.[1] However there was no correlation between the presence of microabscesses and focal signs or seizures. A recent report from the same group of investigators, however, suggested that brain function fails with multiple-organ failure.[8] Our data approximate their findings that showed a significant trend toward lower blood pressures in the severely encephalopathic group.

To date, much of the experimental research has primarily focused on derangements of amino acid profiles that consist of increased levels of the aromatic and sulfur-containing amino acids. This typical pattern in sepsis may be due to an extensive muscle proteolysis that is coupled with a hepatic failure to handle these breakdown products. It has also been postulated that abnormal amino acid transport to the brain causes a disturbance in central nervous system neurotransmitters; this postulate is in keeping with findings in hepatic encephalopathy.[4] Clinical evidence of this possible link is currently absent. Moreover, there are little convincing data concerning clinical efficacy of branched-chain amino acid infusion, which, on the other hand, has been proved to be beneficial in hepatic encephalopathy.[9] We found no significant correlation between sepsis-associated hepatic failure and septic encephalopathy; this finding argues, within limits of this study, against this mechanism.

It has recently been recognized that cerebral blood flow is decreased in sepsis with concordant changes in cerebral oxygen extraction ratios.[9,10] Whether severe hypotension augments the decrease in cerebral perfusion is not clear from the present study. Therefore, it becomes important to know if aggressive control of hypotension early in the course of multiple-organ failure can prevent the development of septic encephalopathy. This may be determined by prospectively studying clinical parameters and neuropathological changes in a large cohort of patients with sepsis. From such a study, further support for diffuse ischemic brain damage related to a severe perfusion deficit may be found.[11] In addition, it seems desirable to study the central nervous system complications in patients with shock syndromes that are associated with high systemic vascular resistance.

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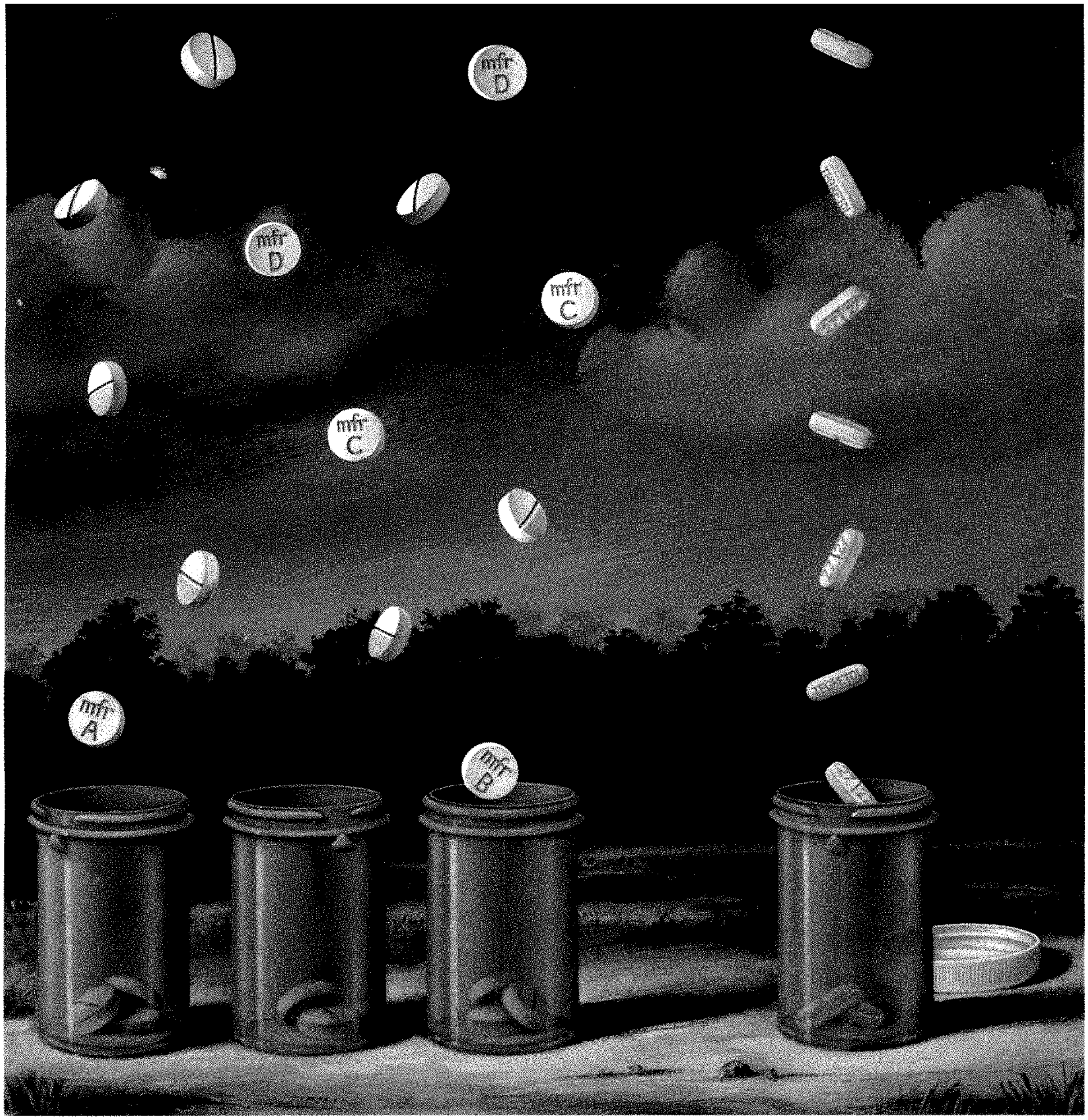

From refill to refill... which carbamazepine will your patient get next?

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the following page, especially the boxed warning.

BASEL

Prevent substitution when you prescribe Tegretol

Sign each prescription on the line that prevents substitution, or add the phrase required in your state to prevent substitution:

☐ Dispense As Written
☐ No Substitution
☐ Do Not Substitute
☐ Brand Necessary
☐ No Drug Product Selection
☐ May Not Substitute
☐ Medically Necessary

For your Medicaid patients...

To prevent substitution of TEGRETOL for your Medicaid patients, be sure to add the phrase "Brand Medically Necessary" on each prescription.

Tegretol®
carbamazepine USP

200-mg scored tablets
100-mg chewable tablets

...because there's no substitute for experience.

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Tegretol®

carbamazepine USP

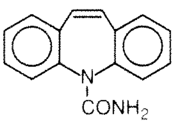
Chewable Tablets of 100 mg—red-speckled, pink
Tablets of 200 mg—pink
Suspension of 100 mg/5 ml

> WARNING
> APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.
>
> ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.
>
> BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, and as a suspension of 100 mg/5 ml (teaspoon). Its chemical name is 5*H*-dibenz[b,f]azepine-5-carboxamide, and its structural formula is:



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Tablets: Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

In clinical studies both suspension and conventional tablet delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster than the tablet. Following a b.i.d. dosage regimen, the suspension has higher peak levels and lower trough levels than those obtained from the tablet formulation for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 µg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 µg/ml. Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4 to 5 hours after administration of oral tablets. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

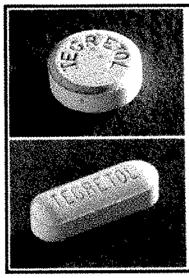
This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.



Only TEGRETOL
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10,11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid, fluoxetine or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated; especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: Either 200 mg b.i.d. for tablets or 1 teaspoon q.i.d. for suspension (400 mg per day). Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: Either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension (200 mg per day). Increase at weekly intervals by adding up to 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg/daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 58887-052-30
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 58887-052-32

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

Bottles of 100	NDC 58887-027-30
Bottles of 1000	NDC 58887-027-40
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 58887-027-32

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture. Dispense in tight container (USP).

Suspension 100 mg/5 ml (teaspoon)—yellow-orange, citrus-vanilla flavored

Bottles of 450 ml	NDC 58887-019-76

Shake well before using.

Do not store above 86°F.

Dispense in tight, light-resistant container (USP).

Printed in U.S.A. C91-50 (Rev. 11/91)

BASEL Pharmaceuticals

BASEL Pharmaceuticals
Division of
CIBA-GEIGY Corporation
Summit, New Jersey 07901

Dosage Information: Tablets and Suspension

Indication	Initial Dose		Subsequent Dose		Maximum Dose
	Tablet	Suspension	Tablet	Suspension	Tablet or Suspension
Epilepsy					
6-12 years of age	100 mg b.i.d. (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 100 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 1 teaspoon (100 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours
Over 12 years of age	200 mg b.i.d. (400 mg/day)	1 teaspoon q.i.d. (400 mg/day)	Add up to 200 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 2 teaspoons (200 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours: 12-15 years 1200 mg/24 hours: over 15 years 1600 mg/24 hours: adults, in rare instances
Trigeminal Neuralgia	100 mg b.i.d. on the first day (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 200 mg per day in increments of 100 mg every 12 hours	Add up to 2 teaspoons (200 mg) per day q.i.d.	1200 mg/24 hours

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Call for Papers

1993 International Conference on Physician Health
January 28-31, 1993. Scottsdale, Arizona

Facing Issues, Seeking Solutions, Advocating Help

The 1993 International Conference on Physician Health, co-sponsored by the American Medical Association, the Federation of State Medical Boards, the Canadian Medical Association, and the Federation of Medical Licensing Authorities of Canada is scheduled for January 28-31, 1993, at the Marriott Mountain Shadows Resort in Scottsdale, Arizona. The conference will provide a forum for practitioners and researchers to present recent findings and innovative treatment and educational programs in the area of physician health. This conference will address a range of issues relative to physicians, including AIDS, the HIV positive physician, problems related to aging, health promotion among physicians, mental illness, physical disability, and substance abuse among physicians. Possible topics for presentation include: incidence of health problems among physicians, the presentation of health problems by physicians, their treatment, the impact of disorders on physician's family and practice, medical-legal implications of various disorders, and the impact of these disorders on hospital administrations. *Abstracts which address issues related to these topics (i.e., diagnosis, treatment, rehabilitation), but not dealing specifically with physicians are also welcome.*

Three types of presentations regarding these physician health issues are invited:

- **Poster Presentations**
Written presentations of data-based research, epidemiological research, or descriptive papers regarding treatment and educational programs.
- **Paper Sessions**
Oral presentation of scientific, data-based findings relative to topic of physician health.
- **Workshops**
Training or instructional presentations, designed to improve specific skill levels of persons who work in the area of physician health.

Abstracts for poster presentations and paper sessions should contain an introductory statement on the significance of subject matter. Description of methods, results, and conclusions should follow the introductory statement.

Abstracts for workshops should contain information on the program's intended audience, goals, teaching strategies, and materials. Evaluation data should be summarized.

Abstract may not exceed *200* words. Any abstracts exceeding that length will be rejected. Abstracts should be typed, double spaced, and mailed (not faxed). Four copies of the abstract should be sent, along with one self-addressed, stamped envelope. All submissions must list the primary and secondary authors and their professional affiliations. Telephone number and address of primary author must also be included.

Paper and Workshop submissions should indicate any audiovisual equipment that is needed.

Submissions *must* be received by June 15, 1992.

Abstracts will be submitted for blind review. Abstracts will be judged on their applicability to the conference topic area and their scientific merit. The decisions of the blind reviewers will be communicated to the abstract's primary author by August 15, 1992.

All persons who have an abstract accepted for presentation at the conference are expected to register for the conference. We are unable to reduce registration fee for presenters, nor are we able to provide any financial support for presenters. All persons who attend the conference will be responsible for their own transportation and hotel expenses, as well as making all reservations for same.

Send all materials to:
Patrick W. McGuffin, PhD, Department of Mental Health, American Medical Association, 515 North State Street, Chicago, IL 60610.

American Medical Association
Physicians dedicated to the health of America

CAFERGOT STOPS MIGRAINE FROM THE START

Aborts migraine before it starts;
stops migraine in progress

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(ergotamine tartrate
and caffeine) Tablets/Suppositories

The choice from the start

SANDOZ

CAFERGOT®

(ergotamine tartrate and caffeine) tablets, USP
(ergotamine tartrate and caffeine) suppositories, USP

DESCRIPTION

Cafergot® (ergotamine tartrate and caffeine) Tablet

ergotamine tartrate USP	1 mg
caffeine USP	100 mg

Inactive Ingredients: acacia, carnauba wax, lactose, methylparaben, povidone, propylparaben, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black ferric oxide, synthetic red ferric oxide, synthetic yellow ferric oxide, talc, tartaric acid, and titanium dioxide.

Cafergot® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP	2 mg
caffeine USP	100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

Cafergot® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage. If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

ACTIONS

Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

INDICATIONS

Cafergot® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia".

CONTRAINDICATIONS

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy.

Hypersensitivity to any of the components.

PRECAUTIONS

Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

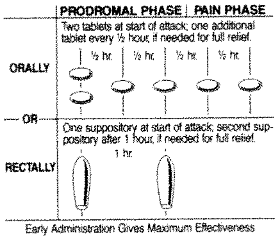
There have been reports of drug abuse and psychological dependence in patients on Cafergot® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism.

ADVERSE REACTIONS

Vasoconstrictive complications, at times of a serious nature, may occur. These include pulselessness, weakness, muscle pains and paresthesias of the extremities and precordial distress and pain. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other adverse effects include transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

DOSAGE AND ADMINISTRATION

Procedure: For the best results, dosage should start at the first sign of an attack.


PRODROMAL PHASE
PAIN PHASE
Two tablets at start of attack; one additional tablet every ½ hour, if needed for full relief.
½ hr.
½ hr.
½ hr.
½ hr.
ORALLY
OR
One suppository at start of attack; second suppository after 1 hour, if needed for full relief.
1 hr.
RECTALLY

Early Administration Gives Maximum Effectiveness

MAXIMUM ADULT DOSAGE

Orally: Total dose for any one attack should not exceed 6 tablets.

Rectally: Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 10 tablets or 5 suppositories.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

OVERDOSAGE

The toxic effects of an acute overdosage of Cafergot® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by induction of emesis, gastric lavage, and catharsis. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

HOW SUPPLIED

Cafergot® (ergotamine tartrate and caffeine) Tablets

Shell pink colored, sugar coated, imprinted "CAFERGOT" on one side, "S" on other side. Bottles of 250, NDC 0078-0034-28, and cartons of three SigPak® (dispensing unit) packages, each containing 30 tablets in individual blisters, NDC 0078-0034-42.

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Sealed in fuchsia-colored aluminum foil, imprinted "S" "CAFERGOT® SUPPOSITORY 78-33 SANDOZ".

RE-INTRODUCE THE OLDEST ADVANCE IN MEDICINES.

It's called talking. If your older patients don't ask you about the prescriptions they've been given, make it a point to tell them what they need to know. Make sure they know the medicine's name, how and when to take it, precautions, and possible side effects. Encourage them to write down the information and ask you questions about things they don't understand.

You'll also want to take a complete medications history including both prescription *and* non-prescription medicines. The history can alert you to the potential for drug interactions and help you simplify their regimen.

Re-introduce the oldest advance in medicines. Make talking a crucial part of your practice. Because good, clear communication about medicines isn't a thing of the past. It's the way to a healthier future.

Before they take it,
talk about it.

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Original Contribution

Mortality From Motor Neuron Disease in the Province of Bologna, Italy, 1986 Through 1988

Salvatore Ferro, MD; Alfonso Giovannini, MD; Laila Fiorani, MD; Pasquale Carmentano, MD; Roberto D'Alessandro, MD

• We performed a study on mortality from motor neuron disease in the province of Bologna, Italy, during the years 1986 through 1988. The study was based on death certificates from the Cancer Registry of the Province of Bologna. We verified death certificates for both false-positive and false-negative cases. The crude mortality rate was 1.93/100 000 population per year. The age and sex mortality rate, standardized on the Italian population, was 1.40/100 000 (95% confidence interval, 1.05 to 1.83). Our figures are higher than those previously reported both as the incidence and as mortality in Italy, but these data are similar to values that have been found in northern Europe and in North America.

(*Arch Neurol.* 1992;49:661-663)

The mortality rate from motor neuron disease (MND) has been widely investigated. It has ranged from 0.61/100 000 population in Iceland to 2.4/100 000 in Sweden.[1-3]

Previous studies on the descriptive epidemiology of MND in Italy showed incidence rates that ranged from 0.63 in Sardinia to 1.20 in Piedmont, (northwestern region) Italy.[4,5] Such rates, which are lower than those reported in northern Europe, suggest that MND may be less frequent in Italy.

The only previous Italian study on MND mortality, performed in the province of Ferrara,[6] showed a rate of 0.83/100 000 population during the period 1964 through 1982, confirming an apparently lower incidence of the disease. Herein, we report the results of a study on mortality from MND in the province of Bologna, Italy, during the years 1986 through 1988, based on verified death certificates (DCs).

MATERIALS AND METHODS

The province of Bologna is located in northeastern Italy; on December 31, 1987, its estimated population was 914 466 inhabitants (438 835 men, 475 631 women).[7]

In 1989, the DCs for the years 1986 through 1988 were available from the Cancer Registry of the Province of Bologna. We obtained all DCs that reported MND as both the primary and underlying cause of death (code 335.2 according to the *International Classification of Diseases [ICD], Ninth Revision*[8]).

False-positive cases were identified by searching clinical records in the Neurologic Clinic of Bologna and other hospitals in the province. In some cases, we had information that patients had been admitted to hospitals outside the province of Bologna, and we obtained these clinical records, when necessary.

False-negative cases were sought out in two ways as follows: (1) We verified the clinical records of cases reported in the DCs under the *ICD* codes 331.8, 331.9, 335.8, 335.9, or 336.9 (ie, other and unspecified cerebral degeneration, diseases of the anterior horn of the spinal cord, or unspecified spinal cord disease) to ascertain whether some cases of MND had been included. (2) We verified the DCs of all patients with MND who were seen at the Neurologic Clinic of Bologna during 1979 through 1988 and who died between 1986 and 1988. We considered false-negative cases as only those in which the cause of death could reasonably be attributed to MND.

The diagnosis of MND was based on the following criteria: progressive course of a motor disorder with wasting, weakness, and fasciculation. Progressive muscular atrophy, progressive bulbar palsy, or amyotrophic lateral sclerosis was diagnosed according to prevalent distribution at spinal skeletal muscles (ie, progressive muscular atrophy) or at bulbar innervated musculature, excluding ocular muscles (ie, progressive bulbar palsy), or with signs of pyramidal tract lesions (ie, amyotrophic laterial sclerosis); absence of sensory defects and sphincter abnormalities was also required. The diagnosis had to be confirmed by a typical electromyographic pattern and, when the clinical picture was atypical, by normal cerebrospinal fluid findings and neuroradiologic examination (ie, myelography, computed tomographic scan, or magnetic resonance imaging).

We calculated mortality rates on the basis of DCs from the cancer registry, corrected for both false-positive and false-negative cases. Cases that were reported as MND in the DCs but for which clinical records were lacking were considered to be MND, to calculate mortality rates.

Mortality rates were calculated for the estimated population of the province of Bologna, as of December 31, 1987, and rates for age and sex were standardized against the Italian (according to the 1981 census), European, and world population.[9] Confidence intervals (CIs) were calculated according to the method of Schoenberg.[10] To correct the possible effect of differing distribution by age between sexes, we also calculated the sex ratio on rates that were standardized for age on the whole population (Italian Census-1981).[11] The z value was computed to test the statistical significance of the relative risks (RRs) (sex ratios) within each age stratum. Furthermore, to compare mortality

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Reprint requests to Clinica Neurologica, Via U Foscolo 7, 40123 Bologna, Italy (Dr D'Alessandro).

Table 1.—Cases With MND Reported With Noncorresponding Codes According to the *ICD**

Patient/ Sex/Age, y	*ICD* Code	Cause
1/M/63.09	431.0	Intracerebral hemorrhage
2/F/73.04	349.8	Other disease of CNS not classified elsewhere
3/M/74.05	803.3	Head trauma
4/M/69.08	188.9	Cancer of the bladder
5/M/62.07	162.9	Lung cancer
6/M/76.04	410.0	Myocardial infarction
7/M/78.01	410.0	Myocardial infarction
8/M/73.02	359.1	Muscular dystrophy
9/F/66.08	403.0	Hypertensive nephropathy
10/M/81.06	491.2	Chronic obstructive lung disease
11/F/66.02	434.0	Stroke

*MND indicates motor neuron disease; *ICD, International Classification of Diseases, Ninth Revision*[8]; and CNS, central nervous system. Data refer to possible false negatives and patients who died of other causes.

rates in the two sexes, we used the Mantel-Haenszel procedure to estimate the overall RR.[12] The CIs of the RR according to the Mantel-Haenszel procedure were calculated according to the methods of Miettinen[13] and Greenland.[14] To verify whether age-related RRs differed from the RR according to the Mantel-Haenszel procedure, we used the χ^2 test for heterogeneity.[15]

RESULTS

The cancer registry reported 55 cases of MND, giving a crude annual mortality rate of 2.0 (95% CI, 1.5 to 2.6; men, 1.89; women, 2.1; and male-female ratio, 0.9).

Among these 55 cases, we found reliable clinical documentation for 52 patients. Five (9.0%) of these cases were proved not to be MND. Therefore, 50 cases remained (three of them on the basis of the DC alone) with a crude mortality rate of 1.82 (95% CI, 1.35 to 2.40; men, 1.59; and women, 2.03).

We found 11 cases of DCs reporting other *ICD* codes considered. None of these were proved to be MND on the basis of clinical documentation. The conditions of 28 patients were diagnosed as MND in the Neurologic Clinic of Bologna, and these patients subsequently died during the study period. Of these deaths, 11 (39.6%) were not certified as MND, but only three (*ICD* codes 349.8, 359.1, and 491.2) were considered to be a misdiagnosis since other causes of death seemed to be unrelated to MND.

Causes of death and *ICD* codes of these cases are shown in Table 1. Adding our three false-negative cases, we obtained a total of 53 patients with MND who died during the study period. On the basis of clinical documentation available, we stated that three cases had progressive muscular atrophy, four had progressive bulbar palsy, and 43 had amyotrophic lateral sclerosis.

Table 2.—Age- and Sex-Specific Mortality Rates in the Province of Bologna, Italy, 1986 Through 1988*

Group Age Range, y	No. of Cases	Population	Rate
Sex, M			
0-34	0	181 746	0
35-44	0	63 005	0
45-54	1	64 215	0.52
55-64	8	61 153	4.36
65-74	8	42 112	6.33
≥75	6	26 604	7.52
Total	**23**	**438 835**	1.75
Sex, F			
0-34	0	173 086	0
35-44	3	64 661	1.55
45-54	5	67 980	2.45
55-64	9	67 834	4.42
65-74	7	54 450	4.28
≥75	6	47 620	4.19
Total	**30**	**475 631**	2.10
Both sexes			
0-34	**0**	**354 832**	0
35-44	**3**	**127 666**	0.78
45-54	**6**	**132 195**	1.51
55-64	**17**	**128 987**	4.39
65-74	**15**	**96 562**	5.17
≥75	**12**	**74 224**	5.38
Total	**53**	**914 466**	1.9

*Rate per 100 000 population per year; estimated population as of December 31, 1987.

Table 3.—Age- and Sex-Adjusted Mortality Rates for the Italian (1981 Census), European, and World Population and 95% CIs*

Standardized Rates	Rate (CI)		
	Men	Women	Both Sexes
Italy (1981 census)	1.24 (0.78-1.86)	1.62 (1.09-2.31)	1.43 (1.07-1.87)
Europe	1.29 (0.82-1.94)	1.50 (1.02-2.16)	1.38 (1.03-1.80)
World	0.87 (0.55-1.30)	1.10 (0.74-1.58)	0.97 (0.72-1.27)

*CI(s) indicates confidence interval(s).

The crude mortality rate for MND in the province of Bologna during 1986 through 1988 was 1.93 (95% CI, 1.44 to 2.53; men, 1.75; women, 2.1; and male-female ratio, 0.83). The mortality rate, adjusted to the Italian population at the 1981 census, was 1.43 (95% CI, 1.04 to 1.83); it was 1.24 (95% CI, 0.77 to 1.90) for men and 1.62 (95% CI, 1.08 to 2.27) for women. Age- and sex-specific mortality rates for MND are shown in Table 2. Age- and sex-adjusted mortality rates are shown in Table 3. The male-female ratio, calculated on sex- and age-adjusted rates in the Italian population, was 0.76, and the corresponding value adjusted for age only was 0.92. The sex ratio by age increased from 0.21 in the group aged from 45 to 54 years to 1.79 among people aged older than 75 years. However, there was no significant difference in either the sex ratio within each age group ($z = -.08$, $P = .94$) or the RR according to the Mantel-Haenszel procedure (0.98; 95% CI, 0.57 to 1.67). Furthermore, the χ^2 test for heterogeneity showed no significant differences in sex ratios by age ($\chi^2 = 2.502$, $P = .64$).

Considering false-positive cases and cases with MND but with DCs reporting other causes (false-negative plus independent deaths), we can attempt to estimate the incidence of disease. Considering 9.0% as the proportion of false positives, 39% as the proportion of unreported MND in the DCs, 2.0 as the crude mortality rate obtained from the cancer registry, and the fact that MND is invariably fatal, an estimated incidence results from the following calculation: $[2.0-(2.0\times0.09)+(2.0\times0.39)]=2.6$.

COMMENT

Our findings were based on DCs, verified for both false-positive and false-negative cases. Mortality rates for MND in the province of Bologna, however, are probably underestimated since to find false-negative cases we reviewed only cases that had been previously seen at the Neurologic Clinic of Bologna: cases that were observed elsewhere may have escaped our survey. Nevertheless, we found mortality rates that were substantially higher than those previously reported in the nearby province of Ferrara. Furthermore, our rates were similar to those reported in England (1.6), Sweden (1.9), southwestern Ontario, Canada (1.52), and Scotland (1.4).[3,16-18]

Mortality rates for MND in the province of Bologna were also higher than incidence rates of MND that were previously reported in Italy, showing that the incidence of the disease has probably been underestimated.

Moreover, in our study, recognition of unreported MND in DCs allowed us to estimate the incidence. Although this finding has to be taken cautiously since it was extrapolated from mortality data, the value that was obtained was very close to that reported in Rochester, Minn.[19] However, it should be noted that our study was performed in a more recent period than previous Italian studies. Since it has been shown that there is a historic trend of rising mortality from MND,[20] it may be that our higher mortality and incidence rates were partially explained by the study period.

In our study, the sex ratio was 0.83, considering age- and sex-specific mortality rates and 0.92 for the age-adjusted rates on the whole Italian population. In any case, these values are considerably lower than those previously reported by most studies. This discrepancy may be explained by underreporting among men in our population or by an underreporting among women in other studies or by a real difference in the male-female ratio in Bologna.

Since we corrected our data for both false-positive and false-negative cases, it seems unlikely that cases of men have been underreported in our study. However, it should be noted that more men than women with MND have been described as apparently dying of unrelated causes in our study. Even considering these cases, the male-female ratio was about 1. Whether other studies underreported mortality for women cannot be stated, but our findings are in agreement with values reported in Finland[21] and France.[22] We did not find significant differences either with regard to the male-female ratio, as computed on age- and sex-adjusted mortality rates, or for the sex ratio within each age stratum and age distribution. However, the male-female ratio increased with age, suggesting that our value may be explained by a higher mortality among younger women. In any case, our findings are in agreement with the hypothesis that there are no sex differences in mortality rates from MND.[23]

With regard to age- and sex-specific mortality rates and the frequency of three clinical pictures of MND, our findings are in agreement with those that have been generally reported.

In conclusion, our study shows that mortality from MND in Italy and probably its incidence are similar to those that have been reported in northern Europe and North America. This finding supports the hypothesis that MND is uniformly distributed throughout the world[24] and makes it unlikely that geographic or environmental factors play a causal role in this disease. Our study also shows that DCs are a reliable means of studying the distribution of MND.

We thank Antonella Pollini for editorial assistance.

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MAUI ORTHOPEDIC and Sports Medicine seeks neurologist to establish independent practice. Contact: William Gfeller, 450 Hookahi Street, Wailuku, Maui, HI 96793. (808) 244-5541.

EXTRAORDINARY OPPORTUNITY – The University of South Florida and the Tampa General Hospital are combining resources to establish a Stroke Service and are recruiting a Service Director. Requirements: Board-eligible/-certified status, stroke expertise, and teaching/scholarly abilities. Rank, salary, and benefits negotiable dependent upon qualifications. Contact: Leon D. Prockop, MD, Chairman, Department of Neurology, (813) 974-2794. MDC Box 55, 12901 Bruce B. Downs Boulevard, Tampa, Florida 33612. USF is an affiliated equal opportunity employer.

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NEUROLOGIST: Excellent opportunity for board-certified/board-eligible neurologists to join two existing neurologists in a stimulating, busy practice. Marquette General Hospital is a 321-bed regional referral center, with a comprehensive neurophsiology department and state-of-the-art technology that includes magnetic resonance imaging and CT scanning, and a hospital-based family practice residency. Medical students from Michigan State University's College of Human Medicine are regularly assigned to the hospital and offer an opportunity for teaching. Marquette General Hospital and its medical staff are committed to building a center of excellence in the neurosciences and have the necessary financial resources. The development of these services will require the leadership and cooperation of physicians in the field of neurology, neurosurgery, psychiatry, physical medicine and rehabilitation. Salaried and private practice positions are available. If this special opportunity is of interest to you, please send CV to: Robert J. Raica, Marquette General Hospital, 420 West Magnetic Street, Marquette, MI 49855.

NEUROLOGIST

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Residencies

NEUROLOGY – Unexpected opening PGYIII-IV to begin July, 1992. Contact: Dr. James Kelly, Box B182, University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver, CO 80262. (303) 270-8760. AA/EOE.

NEUROLOGY RESIDENCY PROGRAM–Dartmouth-Hitchcock Medical Center. PGYIII position available starting July 1, 1992. For information write: Alexander G. Reeves, MD, Professor and Chairman, Section of Neurology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756.

Faculty Positions

EPILEPTOLOGIST: The Department of Neurology at the University of Illinois at Chicago is recruiting an epileptologist at the level of assistant professor. The epileptologist will participate in drug trials for epilepsy, evaluation of epilepsy patients for neurosurgery, out-patient and in-patient management of epilepsy patients, and serve as co-director of an in-patient neuro-psychiatry unit. Candidate must have completed an accredited neurology residency and a fellowship in EEG or epilepsy, and must have special expertise in epilepsy. Contact: Daniel B. Hier, MD, Professor and Head, Department of Neurology, MC 796, University of Illinois at Chicago, Box 6998, Chicago, IL 60608. Or telephone: (312) 996-1757. UIC is an AA/EOE.

NEUROREHABILITATION. A full-time position as Assistant Professor of Clinical Neurology is available July 1, 1992, for a BE/BC neurologist at Rancho Los Amigos Medical Center, a 450 bed rehabilitation hospital closely affiliated with the University of Southern California. We seek a neurologist who is interested in clinical care and teaching in neurologic rehabilitaion. There is an active USC-affiliated neurology resident training program, excellent opportunities for clinical research, regular hours, and limited on-call responsibilities. Send CV to: Helena Chui, MD, Department of Neurological Sciences, 700 Annex, 7601 East Imperial Highway, Downey, CA 90242. Both USC and Rancho are EOE/AA employers.

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The Department of Neurology at Temple University School of Medicine seeks a Neuroimmunologist for a faculty position at the Assistant Professor level. Candidates should be board certified/board eligible in neurology with completed immunology fellowship training. Molecular biology experience is desired. The applicant will be expected to establish a research program in molecular immunology and to participate in activities of the Multiple Sclerosis Center. Research support is available. Applications should be forwarded to: **Jeffrey I. Greenstein, M.D., Chair, Department of Neurology, TEMPLE UNIVERSITY SCHOOL OF MEDICINE, 3401 N. Broad Street, Philadelphia, PA 19140.**

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Fellowships

CLINICAL NEUROPHYSIOLOGY/Epilepsy/Sleep Disorders Combined Fellowship – Offered for 1-2 years beginning July 1, 1992 at New England Medical Center and Tufts University School of Medicine, Boston, Massachusetts. The program offers training in pediatric/adult clinical EEG (including established computer techniques), drug studies in epilepsy and sleep disorders, video-EEG telemetry monitoring, presurgical cortical stimulation, intraoperative electrocorticography, polysomnography, and sleep disorders medicine (including neurology, psychiatry, ENT and pulmonary medicine). Candidates must be board-eligible in neurology and meet requirements for Massachusetts licensure. Applicants should send their CV and three references to: Bruce L. Ehrenberg, MD, New England Medical Center, EEG Department, 750 Washington Street, Boston, MA 02111; or call (617) 956-7504. New England Medical Center and Tufts University are affirmative action/equal opportunity employers.

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EMG FELLOWSHIP – We are now excepting applications for one or two year positions beginning in July 1993 at the Brigham and Women's Hospital, Boston, Massachusetts. Applicants should be recent graduates of a neurology training program. Send CV and three letters of recommendation to: Dr. E. Logigian, Division of Neurology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

Positions Wanted

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Abstracts which address issues related to these topics, but not dealing specifically with physicians are also welcome.

Submission Deadline: June 15, 1992.

Contact:
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ANNUAL MEETING AND COURSES

American Electroencephalographic Society
September 16-20, 1992
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The **Annual Meeting** of the Society will be held September 18-20 at the Fairmont Hotel in San Francisco. The program will include Symposia on: **Recovery of Function Following Injury To Essential Cortical Areas, Intraoperative Neurophysiological Monitoring, Digital EEG: What It Does and What We Would Like It To Do**, as well as Scientific Sessions, posters, and a technical exhibit.

The meeting will be preceded on Friday morning, September 18 by a special workshop that will bring together leading experts on new and advanced techniques for the measurement of cerebral function.

The **Annual Courses** of the Society will be held September 16-18 at the Fairmont Hotel. Courses include: **Basic EEG** (full-day), **Sleep Disorders, Basic EMG, Evoked Potentials, Neurophysiology**, and **Neonatal EEG**.

The American EEG Society is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

For more information, contact:

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Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See "Warnings" section for information on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, and immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Caution – Federal law prohibits dispensing without prescription. 0362G280

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References **1.** Data on file, Market Research Dept, Parke-Davis. **2.** Ramsay RE, Wilder BJ, Berger JR, Bruni J. A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology.* 1983;33:904-910. **3.** Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin T. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *J Neurol Neurosurg Psychiatry.* 1985;48:639-644. **4.** Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med.* 1985;313:145-151.

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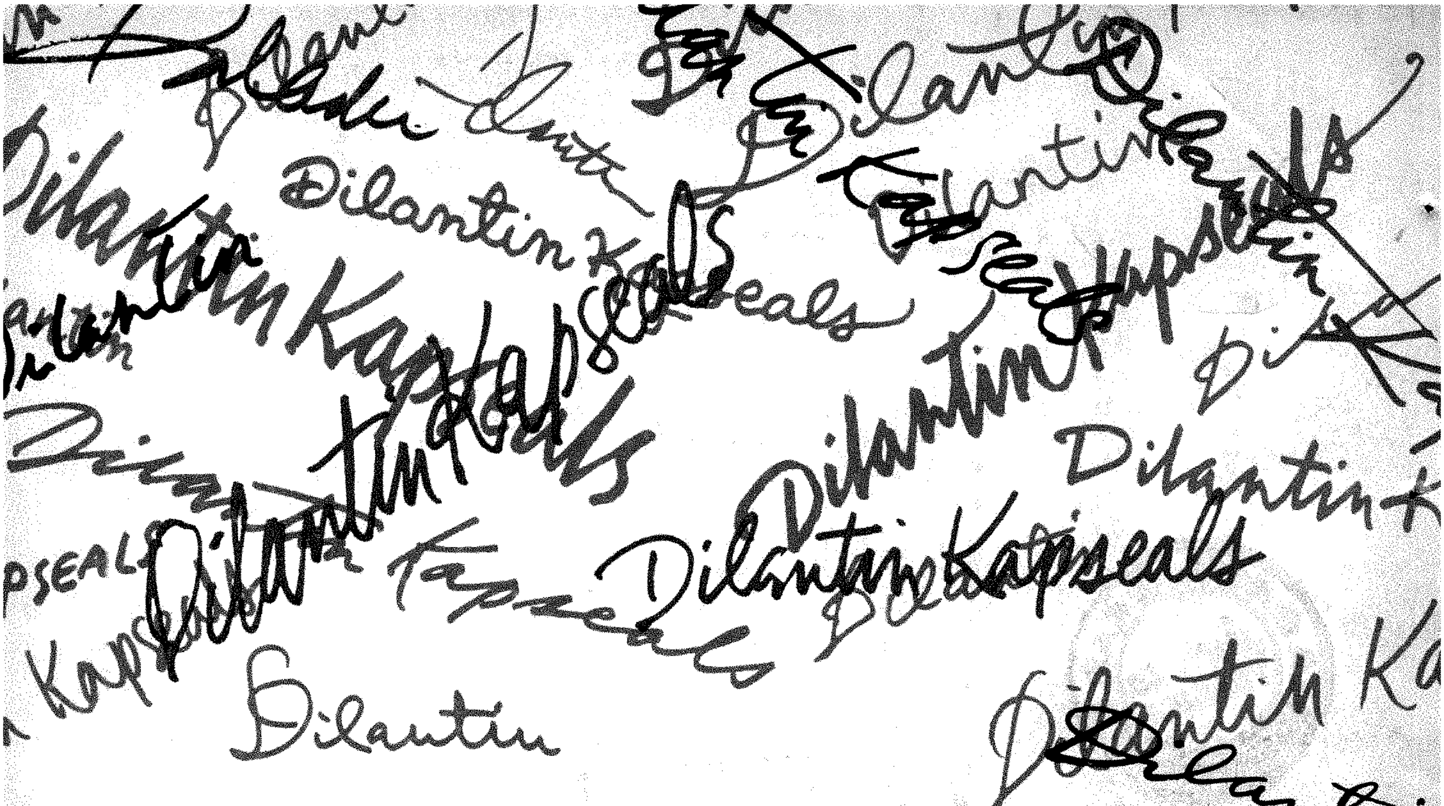

Thousands of neurologists go by the same name.

Neurologists write "Dilantin" more often than any other name in anticonvulsant therapy[1]—and for good reasons:

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- **Convenient once-daily dosing for many patients***
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When you add billions of successful patient therapy days, it's clear why so many neurologists independently write the same prescription: Dilantin Kapseals for effective seizure control.

*For adult patients already controlled on 100 mg tid of Dilantin Kapseals.
†Adapted from *IMS National Pharmacy Audit Basic Data Book*, 4/91-6/91.[1]
Please see next page for a brief summary of full prescribing information.

Dilantin® Kapseals®

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Volume 49, Number 7

American Medical Association
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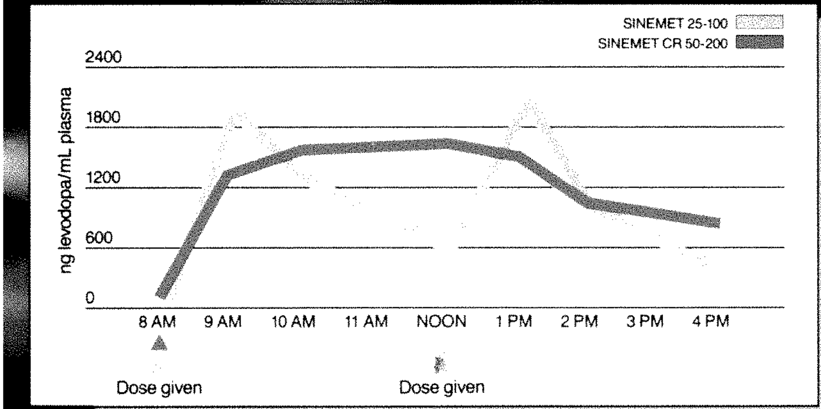
For many patients with
Parkinson's disease

More Quality Time*

The causes of motor fluctuations are not completely understood; *in some patients* they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.



Smoother plasma levodopa levels†[1]

Less fluctuation of plasma levodopa levels with SINEMET CR vs SINEMET® (Carbidopa-Levodopa)

In a clinical trial, 14 patients with mild to moderate Parkinson's disease had plasma levodopa levels measured over 8 hours after one dose of SINEMET CR, and were compared with levels over the same period after two doses of SINEMET 25-100.

SINEMET® CR
(CARBIDOPA-LEVODOPA)
SUSTAINED-RELEASE

Before prescribing SINEMET CR, please see a Brief Summary of Full Prescribing Information on the third page of this advertisement.

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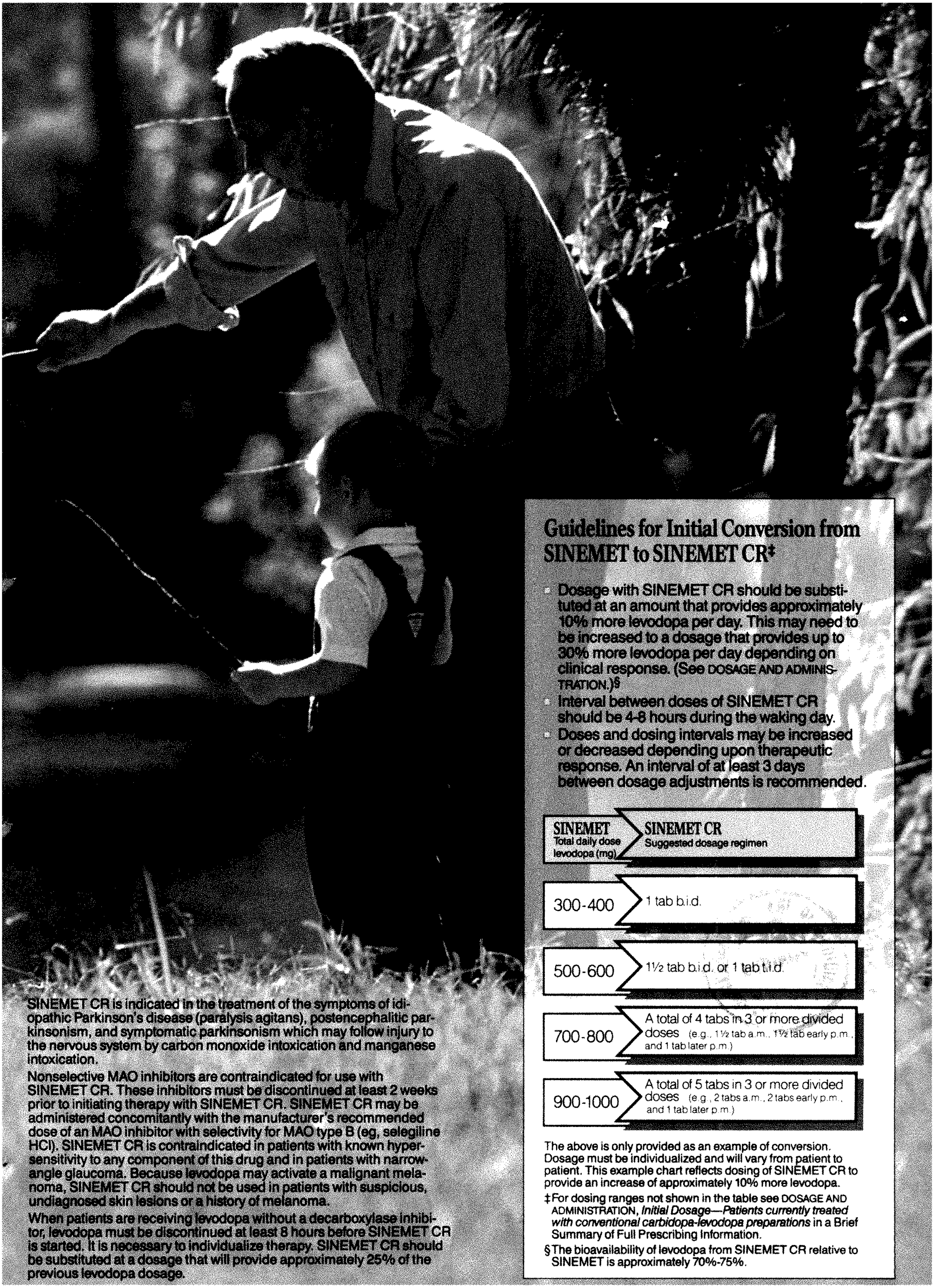
* Although in clinical trials, patients with moderate to severe motor fluctuations who received SINEMET® CR (Carbidopa-Levodopa) Sustained-Release *did not experience quantitatively significant reductions* in "off" time when compared to SINEMET, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET.

† Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET. The physician should be notified if such delayed responses pose a problem in treatment.

1. Goetz CG, Tanner CM, Shannon KM, et al. Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuations. *Neurology*.



Guidelines for Initial Conversion from SINEMET to SINEMET CR‡

- Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day. This may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response. (See DOSAGE AND ADMINISTRATION.)§
- Interval between doses of SINEMET CR should be 4-8 hours during the waking day.
- Doses and dosing intervals may be increased or decreased depending upon therapeutic response. An interval of at least 3 days between dosage adjustments is recommended.

SINEMET Total daily dose levodopa (mg)	**SINEMET CR** Suggested dosage regimen
300-400	1 tab b.i.d.
500-600	1½ tab b.i.d. or 1 tab t.i.d.
700-800	A total of 4 tabs in 3 or more divided doses (e.g., 1½ tab a.m., 1½ tab early p.m., and 1 tab later p.m.)
900-1000	A total of 5 tabs in 3 or more divided doses (e.g., 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

The above is only provided as an example of conversion. Dosage must be individualized and will vary from patient to patient. This example chart reflects dosing of SINEMET CR to provide an increase of approximately 10% more levodopa.

‡For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage—Patients currently treated with conventional carbidopa-levodopa preparations* in a Brief Summary of Full Prescribing Information.

§The bioavailability of levodopa from SINEMET CR relative to SINEMET is approximately 70%-75%.

SINEMET CR is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication.

Nonselective MAO inhibitors are contraindicated for use with SINEMET CR. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (eg, selegiline HCl). SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma. Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least 8 hours before SINEMET CR is started. It is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage.

SINEMET® CR (CARBIDOPA-LEVODOPA)
SUSTAINED-RELEASE TABLETS

CONTRAINDICATIONS Nonselective MAO inhibitors are contraindicated for use with SINEMET*CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl).

SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least eight hours before SINEMET CR is started. In order to reduce adverse reactions, it is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION).

Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, will occur at lower dosages and sooner during therapy with SINEMET CR (Carbidopa-Levodopa, Sustained-Release) than with levodopa alone.

As with levodopa, SINEMET CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution. The occurrence of dyskinesias may require dosage reduction.

Patients receiving SINEMET CR may develop increased dyskinesia compared to SINEMET (Carbidopa-Levodopa).

SINEMET CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET CR to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET CR may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

PRECAUTIONS General As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET CR provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Information for Patients The patient should be informed that SINEMET CR is a sustained-release formulation of carbidopa-levodopa which releases these ingredients over a 4 to 6 hour period. It is important that SINEMET CR be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

If abnormal involuntary movements appear or get worse during treatment with SINEMET CR, the physician should be notified, as dosage adjustment may be necessary.

Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET (Carbidopa-Levodopa). The physician should be notified if such delayed responses pose a problem in treatment.

Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.

NOTE: The suggested advice to patients being treated with SINEMET CR is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Laboratory Tests Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa-levodopa preparations than with levodopa.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions *Caution should be exercised when the following drugs are administered concomitantly with SINEMET CR (Carbidopa-Levodopa, Sustained-Release).*

Symptomatic postural hypotension has occurred when carbidopa-levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with SINEMET CR is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET CR should be carefully observed for loss of therapeutic response.

Carcinogenesis, Mutagenesis, Impairment of Fertility In a two-year bioassay of SINEMET (Carbidopa-Levodopa), no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

In reproduction studies with SINEMET (Carbidopa-Levodopa), no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

Pregnancy Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET (Carbidopa-Levodopa). There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. SINEMET (Carbidopa-Levodopa) caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. Use of SINEMET CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINEMET CR is administered to a nursing mother.

Pediatric Use Safety and effectiveness in infants and children have not been established, and use of the drug in patients below the age of 18 is not recommended.

ADVERSE REACTIONS In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations while on SINEMET (Carbidopa-Levodopa) were randomized to therapy with either SINEMET (Carbidopa-Levodopa) or SINEMET CR. The adverse experience frequency profile of SINEMET CR did not differ substantially from that of SINEMET (Carbidopa-Levodopa), as shown in Table 1.

Table 1 Clinical Adverse Experiences Occurring in 1% or Greater of Patients

	SINEMET CR	**SINEMET** (Carbidopa-Levodopa)
	n=491	n=524
Adverse Experience	%	%
Dyskinesia	16.5	12.2
Nausea	5.5	5.7
Hallucinations	3.9	3.2
Confusion	3.7	2.3
Dizziness	2.9	2.3
Depression	2.2	1.3
Urinary Tract Infection	2.2	2.3
Headache	2.0	1.9
Dream Abnormalities	1.8	0.8
Dystonia	1.8	0.8
Vomiting	1.8	1.9
Upper Respiratory Infection	1.8	1.0
Dyspnea	1.6	0.4
'On-Off' Phenomena	1.6	1.1
Back Pain	1.6	0.6
Dry Mouth	1.4	1.1
Anorexia	1.2	1.1
Diarrhea	1.2	0.6
Insomnia	1.2	1.0
Orthostatic Hypotension	1.0	1.1
Shoulder Pain	1.0	0.6
Chest Pain	1.0	0.8
Muscle Cramps	0.8	1.0
Paresthesia	0.8	1.1
Urinary Frequency	0.8	1.1
Dyspepsia	0.6	1.1
Constipation	0.2	1.5

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received SINEMET CR and 475 who received SINEMET (Carbidopa-Levodopa) during controlled clinical trials included: decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.

The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with SINEMET CR, listed by body system in order of decreasing frequency, include:

Nervous System/Psychiatric: Chorea, somnolence, falling, anxiety disorder, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.

Body as a Whole: Asthenia, fatigue, abdominal pain, orthostatic effects.

Digestive: Gastrointestinal pain, dysphagia, heartburn.

Cardiovascular: Palpitation, essential hypertension, hypotension, myocardial infarction.

Special Senses: Blurred vision.

Metabolic: Weight loss.

Skin: Rash.

Respiratory: Cough, pharyngeal pain, common cold.

Urogenital: Urinary incontinence.

Musculoskeletal: Leg pain.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

Other adverse experiences have been reported with various carbidopa-levodopa formulations and may occur with SINEMET CR:

Nervous System/Psychiatric: Mental changes including paranoid ideation, psychotic episodes, depression with suicidal tendencies and dementia; convulsions (however, a causal relationship has not been established); bradykinetic episodes.

Gastrointestinal: Gastrointestinal bleeding, development of duodenal ulcer.

Cardiovascular: Cardiac irregularities, phlebitis.

Hematologic: Hemolytic and nonhemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.

Laboratory Tests: Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, protein-bound iodine, Coombs test.

Other adverse reactions that have been reported with levodopa are:

Nervous System: Numbness, increased hand tremor, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome.

Psychiatric: Delusions, euphoria.

Gastrointestinal: Bitter taste, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.

Metabolic: Weight gain, edema.

Integumentary: Malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, loss of hair.

Genitourinary: Urinary retention, urinary incontinence, dark urine, priapism.

Miscellaneous: Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE Management of acute overdosage with SINEMET CR is the same as with levodopa. Pyridoxine is not effective in reversing the actions of SINEMET CR.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET CR should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION SINEMET CR tablets contain carbidopa (50 mg) and levodopa (200 mg) in a 1:4 ratio. The daily dosage of SINEMET CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of involuntary movements, dyskinesias or nausea. SINEMET CR may be administered as whole or as half-tablets which should not be chewed or crushed.

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while SINEMET CR is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Initial Dosage *Patients currently treated with conventional carbidopa-levodopa preparations:* Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see DOSAGE AND ADMINISTRATION, TITRATION). The interval between doses of SINEMET CR should be 4-8 hours during the waking day. *Patients currently treated with levodopa without a decarboxylase inhibitor:* Levodopa must be discontinued at least eight hours before therapy with SINEMET CR is started. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET CR b.i.d. *Patients not receiving levodopa:* In patients with mild to moderate disease, the initial recommended dose is 1 tablet of SINEMET CR b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with 2 to 8 tablets per day, administered as divided doses at intervals ranging from 4 to 8 hours during the waking day. Higher doses (12 or more tablets per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day.

An interval of at least 3 days between dosage adjustments is recommended.

Maintenance Because Parkinson's disease is progressive, periodic clinical evaluations are recommended; adjustment of the dosage regimen of SINEMET CR may be required.

Addition of Other Antiparkinson Medications Anticholinergic agents, dopamine agonists, and amantadine can be given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added.

A dose of SINEMET (Carbidopa-Levodopa) 25-100 or 10-100 (one half or a whole tablet) can be added to the dosage regimen of SINEMET CR in selected patients with advanced disease who need additional levodopa for a brief time during daytime hours.

Interruption of Therapy Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET CR is required, especially if the patient is receiving neuroleptics. (See WARNINGS).

If general anesthesia is required, SINEMET CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED SINEMET CR 50-200 (Carbidopa-Levodopa) SUSTAINED-RELEASE TABLETS containing 50 mg of carbidopa and 200 mg of levodopa, are peach-colored, oval, scored, biconvex, compressed tablets, coded 521. They are supplied as follows:

NDC 0056-0521-68 bottles of 100

NDC 0056-0521-28 unit dose packages of 100.

Storage Avoid temperatures above 30°C (86°F). Store in a tightly closed container.

A.H.F.S. Category: 92:00 Issued June 1991 Printed in U.S.A.

Manufactured by:

MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA
FOR:

DU PONT PHARMA

Du Pont Pharmaceuticals
Wilmington, DE 19880-0026

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Brief Summary of 6251-3/7619403 CR-31238

TABLETS

SINEMET® (CARBIDOPA-LEVODOPA)

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS (below) and DOSAGE AND ADMINISTRATION sections in the Prescribing Information before initiating therapy.

INDICATIONS: SINEMET is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication. SINEMET is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B_6).

The incidence of levodopa-induced nausea and vomiting is less with SINEMET than with levodopa. In many patients this reduction in nausea and vomiting will permit more rapid dosage titration.

In some patients a somewhat smoother antiparkinsonian effect results from therapy with SINEMET than with levodopa. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from SINEMET.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Although the administration of carbidopa permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa. *Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, may occur at low dosages and sooner during therapy with SINEMET than with levodopa.*

Certain patients who responded poorly to levodopa have improved when SINEMET was substituted. This is most likely due to decreased peripheral decarboxylation of levodopa which results from administration of carbidopa rather than to a primary effect of carbidopa on the nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa in parkinsonian syndromes.

In considering whether to give SINEMET to patients already on levodopa who have nausea and/or vomiting, the practitioner should be aware that, while many patients may be expected to improve, some do not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing SINEMET with levodopa, about half of the patients with nausea and/or vomiting on levodopa improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

CONTRAINDICATIONS: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See DOSAGE AND ADMINISTRATION section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

PRECAUTIONS: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS (above).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

ADVERSE REACTIONS: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitation, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred.

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, protein-bound iodine, and Coombs test.

Other adverse reactions that have been reported with levodopa are: *Nervous System:* ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome. *Psychiatric:* confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria. *Gastrointestinal:* dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue. *Metabolic:* weight gain or loss, edema. *Integumentary:* malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, skin rash, loss of hair. *Genitourinary:* urinary retention, urinary incontinence, dark urine, priapism. *Special Senses:* diplopia, blurred vision, dilated pupils, oculogyric crises. *Miscellaneous:* weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

HOW SUPPLIED: Tablets SINEMET 10-100, SINEMET 25-100, and SINEMET 25-250 are supplied in bottles of 100 and unit dose packages of 100.

Storage: Tablets SINEMET 10-100 and Tablets SINEMET 25-250 must be protected from light.

Manufactured by:

MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA
FOR:

DU PONT PHARMA

Du Pont Pharmaceuticals
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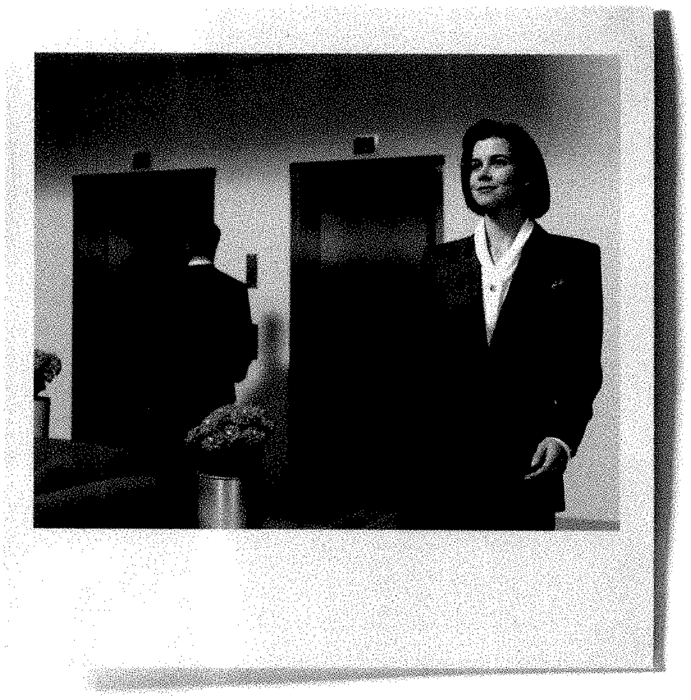

A proven combination for the symptom complex of tension headache, including the pain-relieving potency of codeine.

Please see brief summary of prescribing information on following page.

FIORINAL® WITH CODEINE CAPSULES CIII

(Each capsule contains: codeine phosphate 30 mg; [Warning: May be habit-forming], butalbital 50 mg; [Warning: May be habit-forming], caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

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FWC-0192-01 2/92

BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE CIII CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming]; butalbital USP, 50 mg [warning: may be habit forming]; caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset, lightheadedness and heavy eyelids, and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiorinal® with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	**Fiorinal®/Codeine (N = 382)**	**Placebo (N = 377)**
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caused by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® with Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorinal® with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overdosage is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion, and coma; respiratory depression, hypotension, shock. Symptoms attributable to *acute aspirin poisoning* include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus, hyperthermia, hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® with Codeine. However, because strategies for the management of an overdose continually evolve, consultation with a regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g
Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)
Caffeine: toxic dose greater than 1.0 g; lethal dose unknown
Codeine: lethal dose 0.5-1.0 g (adult)

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EAST HANOVER, NEW JERSEY 07936

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Type A

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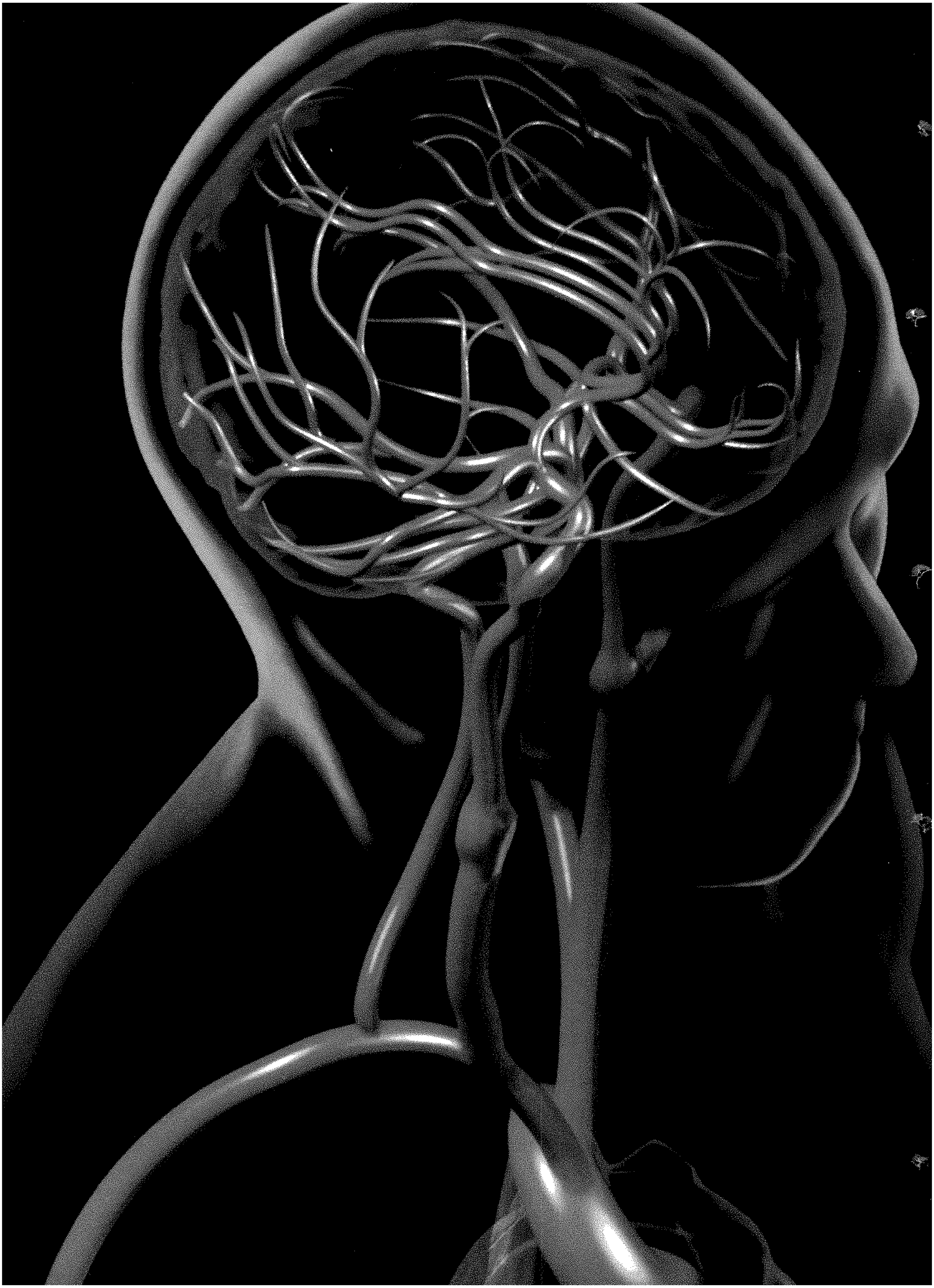
Stroke Devastates.

Today, Significantly Reduce the Risk of Stroke.



Introducing the First Prescription Antiplatelet Agent that Significantly Reduces the Risk of Stroke[1,2]

Ticlid®

Ticlopidine HCl 250mg
Tablets bid

Clinical Trials Demonstrated:

48% reduction vs aspirin[3] in risk of initial stroke in TIA* patients at year 1 (P = .0004, n = 3034), the year of greatest risk

33% reduction in risk[2,4] of fatal or nonfatal recurrent stroke at year 1 (P = .008, n = 1053), the year of greatest risk

Proven effective in women as well as men[1,2,3,4]

Indications

Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life threatening (see Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke

TICLID, therefore, is appropriate first-line therapy for reducing the risk of thrombotic stroke in:
— all female TIA patients
— all males at risk for recurrent stroke
— all females at risk for recurrent stroke
— all aspirin-intolerant male TIA patients

Side Effects

In clinical trials, neutropenia† occurred in a total of 2.4% of patients (0.8% severe‡) and was not typically associated with clinical signs or symptoms

Therefore, CBC monitoring (including differentials) for neutropenia is essential every 2 weeks for the first 3 months of therapy

The most frequently occurring side effects involved the GI tract: diarrhea (12.5%), nausea (7.0%), dyspepsia (7.0%); rash also occurred (5.1%)

Although most side effects were mild, 21% of patients discontinued therapy due to an adverse event in clinical trials

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*Analysis based on all study participants, which included patients with transient ischemic attack, transient monocular blindness, reversible ischemic neurological deficit, and minor stroke
†Defined as <1200 neutrophils/mm^3, seen in 50/2048 patients
‡Defined as <450 neutrophils/mm^3, seen in 17/2048 patients

1. Hass WK, Easton JD, Adams HP Jr et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med.* 1989;321(8):501-507. **2.** Gent M, Easton JD, Hachinski VC et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet.* 1989;1:1215-1220. **3.** TICLID (ticlopidine HCl) tablets full prescribing information. **4.** Biller J, Love BB, Gordon DL. Antithrombotic therapy for ischemic cerebrovascular disease. *Semin Neurol* 1991;11(4):353-367.

Please see brief summary of prescribing information on last page.

SYNTEX

Ticlid

Ticlopidine HCl 250mg Tablets bid

The First Prescription Antiplatelet Agent that Significantly Reduces the Risk of Stroke

For further information, including the CBC Monitoring Program for TICLID, please call 1-800-TICLID-1.

TICLID® (ticlopidine hydrochloride) 250 mg Tablets

INDICATIONS AND USAGE TICLID is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life-threatening (See Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke. **CONTRAINDICATIONS** The use of TICLID® is contraindicated in the following conditions: Hypersensitivity to the drug. Presence of hematopoietic disorders such as neutropenia and thrombocytopenia. Presence of a hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding). Patients with severe liver impairment.

WARNINGS

Neutropenia

Neutropenia defined in these studies as an ANC <1200 neutrophils/mm^3 occurred in 50 of 2,048 (2.4%) stroke patients who received TICLID in clinical trials. *Severe Neutropenia (<450 neutrophils/mm^3)*: Severe neutropenia and/or agranulocytosis occurred in 17 of the 2,048 (0.8%) patients who received TICLID. When the drug was discontinued in these patients, the neutrophil counts returned to normal (>1200 neutrophils/mm^3) within 1-3 weeks. *Mild to Moderate Neutropenia (451-1200 neutrophils/mm^3)*: Mild to moderate neutropenia occurred in 33 of the 2,048 (1.6%) patients who received TICLID. Eleven of the patients discontinued treatment and recovered within a few days. In the remaining 22 patients, the neutropenia was transient and did not require discontinuation of therapy. The onset of severe neutropenia occurred 3 weeks to 3 months after the start of therapy with TICLID, with no documented cases of severe neutropenia beyond that time in the large controlled trials. The bone marrow typically showed a reduction in myeloid precursors. It is therefore essential that CBCs and white cell differentials be performed every two weeks starting from the second week to the end of the third month of therapy with TICLID, but more frequent monitoring is necessary for patients whose absolute neutrophil counts have been consistently declining or are 30% less than the baseline count. Neutropenia (an absolute neutrophil count (ANC) of less than 1200 neutrophils/mm^3) is calculated as follows: ANC = WBC × % neutrophils. If clinical evaluation and repeat laboratory testing confirm the presence of neutropenia (<1200/mm^3), the drug should be discontinued. In clinical trials, when therapy was discontinued immediately upon detection of neutropenia, the neutrophil counts returned to normal within 1-3 weeks. After the first three months of therapy, CBCs need be obtained only for patients with signs or symptoms suggestive of infection.

Thrombocytopenia Rarely, thrombocytopenia may occur in isolation or together with neutropenia. If clinical evaluation and repeat laboratory testing confirm the presence of thrombocytopenia (<80,000 cells/mm^3), the drug should be discontinued. Cholesterol Elevation TICLID® therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8-10% within one month of therapy and persist at that level. The ratios of the lipoprotein subfractions are unchanged. **Other Hematological Effects** Rare cases of pancytopenia and thrombotic thrombocytopenic purpura, some of which have been fatal, have been reported in Post-Marketing Surveillance. **Anticoagulant Drugs** The tolerance and safety of coadministration of TICLID with heparin, oral anticoagulants, or fibrinolytic agents has not been established. If a patient is switched from an anticoagulant or fibrinolytic drug to TICLID, the former drug should be discontinued prior to TICLID administration. **PRECAUTIONS General** TICLID should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or pathological conditions. If it is desired to eliminate the antiplatelet effects of TICLID prior to elective surgery, the drug should be discontinued 10-14 days prior to surgery. Several controlled clinical studies have found increased surgical blood loss in patients undergoing surgery during treatment with ticlopidine. In TASS and CATS it was recommended that patients have ticlopidine discontinued prior to elective surgery. Several hundred patients underwent surgery during the trials, and no excessive surgical bleeding was reported. Prolonged bleeding time is normalized within two hours after administration of 20 mg methylprednisolone i.v. Platelet transfusions may also be used to reverse the effect of TICLID on bleeding. **GI Bleeding** TICLID prolongs template bleeding time. The drug should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients on TICLID. (See Contraindications.) **Use in Hepatically Impaired Patients** Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of TICLID is not recommended in this population. (See Clinical Pharmacology and Contraindications.) **Use in Renally Impaired Patients** There is limited experience in patients with renal impairment. In controlled clinical trials, no unexpected problems have been encountered in patients having mild renal impairment and there is no experience with dosage adjustment in patients with greater degrees of renal impairment. Nevertheless, for renally impaired patients it may be necessary to reduce the dosage of ticlopidine or discontinue it altogether, if hemorrhagic or hematopoietic problems are encountered. (See Clinical Pharmacology) **Information for the Patient (See PPI)** Patients should be told that a decrease in the number of white blood cells (neutropenia) can occur with TICLID® especially during the first three months of treatment, and that if neutropenia is severe, it could result in an increased risk of infection. They should be told it is critically important to obtain the scheduled blood tests to detect neutropenia. Patients should also be reminded to contact their physicians if they experience any indication of infection such as fever, chills, and sore throat, all of which may be consequences of neutropenia. All patients should be told that it may take them longer than usual to stop bleeding when they take TICLID and that they should report any unusual bleeding to their physician. Patients should tell physicians and dentists that they are taking TICLID before any surgery is scheduled and before any new drug is prescribed. Patients should be told to report promptly side effects of TICLID such as severe or persistent diarrhea, skin rashes or subcutaneous bleeding, or any signs of cholestasis, such as yellow skin or sclera, dark urine, or light colored stools. Patients should be told to take TICLID with food or just after eating in order to minimize gastrointestinal discomfort. **Laboratory Tests** *Liver Function* TICLID therapy has been associated with elevations of alkaline phosphatase and transaminases which generally occurred within 1-4 months of therapy initiation. In controlled clinical trials, the incidence of elevated alkaline phosphatase (greater than 2 times upper limit of normal) was 7.6% in ticlopidine patients, 6.0% in placebo patients and 2.5% in aspirin patients. The incidence of elevated AST (SGOT) (greater than 2 times upper limit of normal) was 3.1% in ticlopidine patients, 4.0% in placebo patients and 2.1% in aspirin patients. No progressive increases were observed in closely monitored clinical trials (e.g. no transaminase greater than 10 times the upper limit of normal was seen), but most patients with these abnormalities had therapy discontinued. Occasionally patients had developed minor elevations in bilirubin. Based on post-marketing and clinical trials experiences, liver function testing should be considered whenever liver dysfunction is suspected, particularly during the first four months of treatment. **Drug Interactions** Therapeutic doses of TICLID caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios, or being given to patients with hepatic impairment, may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine. Studies of specific drug interactions yielded the following results. ***Aspirin:*** Aspirin did not modify the ticlopidine-mediated inhibition of ADP-induced platelet aggregation, but ticlopidine potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of this combination has not been established and concomitant use of aspirin and ticlopidine is not recommended. (See Precautions – GI Bleeding). ***Antacids:*** Administration of TICLID after antacids resulted in an 18% decrease in plasma levels of ticlopidine. ***Cimetidine:*** Chronic administration of cimetidine reduced the clearance of a single dose of TICLID by 50%. ***Digoxin:*** Co-administration of TICLID with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected. ***Theophylline:*** In normal volunteers, concomitant administration of TICLID resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hr and a comparable reduction in total plasma clearance of theophylline. ***Phenobarbital:*** In six normal volunteers, the inhibitory effects of TICLID on platelet aggregation were not altered by chronic administration of phenobarbital. ***Phenytoin:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID and it may be useful to remeasure phenytoin blood concentrations. ***Propranolol:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID.

℞

TICLID 250 mg
#30
Sig: 1 Tab bid
with meals

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, TICLID was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs without evidence of clinically significant adverse interactions. (See Precautions.) **Food Interaction:** The oral bioavailability of ticlopidine is increased by 20% when taken after a meal. Administration of TICLID with food is recommended to maximize gastrointestinal tolerance. In controlled trials, TICLID was taken with meals. **Carcinogenesis, Mutagenesis, Impairment of Fertility** In a two-year oral carcinogenicity study in rats, ticlopidine at daily doses of up to 100 mg/kg (610 mg/m^2) was not tumorigenic. For a 70 kg person (1.73m^2 body surface area), the dose represents 14 times the recommended clinical dose on a mg/kg basis and 2 times the clinical dose on body surface area basis. In a 78 week oral carcinogenicity study in mice ticlopidine at daily doses up to 275 mg/kg (1180 mg/m^2) was not tumorigenic. The dose represents 40 times the recommended clinical dose on a mg/kg basis and 4 times the clinical dose on body surface area basis. Ticlopidine was not mutagenic in *in vitro* Ames test, rat hepatocyte DNA-repair assay, and Chinese hamster fibroblast chromosomal aberration test and *in vivo* mouse spermatozoid morphology test, Chinese hamster micronucleus test and Chinese hamster bone marrow cell sister chromatid exchange test. Ticlopidine was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day. **Pregnancy: Teratogenic Effects** Pregnancy Category B. Teratology studies have been conducted in mice (doses up to 200 mg/kg/day), rats (doses up to 400 mg/kg/day) and rabbits (doses up to 200 mg/kg/day). Doses of 400 mg/kg in rats, 200 mg/kg/day in mice, and 100 mg/kg in rabbits produced maternal toxicity as well as fetal toxicity, but there was no evidence of a teratogenic potential of ticlopidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers** Studies in rats have shown ticlopidine is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ticlopidine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** Safety and efficacy in patients under the age of 18 have not been established. **Geriatric Use** Clearance of ticlopidine is somewhat lower in elderly patients and trough levels are increased. The major clinical trials with TICLID were conducted in an elderly population with an average age of 64 years. Of the total number of patients in the therapeutic trials, 45% of patients were over 65 years old and 12% were over 75 years old. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse reactions were relatively frequent, with over 50% of patients reporting at least one. Most (30 to 40%) involved the gastrointestinal tract. Most adverse effects are mild, but 21% of patients discontinued therapy because of an adverse event, principally diarrhea, rash, nausea, vomiting, G.I. pain, and neutropenia. Most adverse effects occur early in the course of treatment, but a new onset of adverse effects can occur after several months. The incidence rates of adverse events listed in the following table were derived from multicenter, controlled clinical trials described above comparing TICLID, placebo, and aspirin over study periods of up to 5.8 years. Adverse events considered by the investigator to be probably drug-related that occurred in at least one percent of patients treated with TICLID are shown in the following table:

Percent of Patients with Adverse Events in Controlled Studies

Event	TICLID (n = 2048) Incidence	Aspirin (n = 1527) Incidence	Placebo (n = 536) Incidence
Any Events	*60.0(20.9)*	*53.2(14.5)*	*34.3 (6.1)*
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	1.7 (0.9)
Dyspepsia	7.0 (1.1)	9.0 (2.0)	0.9 (0.2)
Rash	5.1 (3.4)	1.5 (0.8)	0.6 (0.9)
GI Pain	3.7 (1.9)	5.6 (2.7)	1.3 (0.4)
Neutropenia	2.4 (1.3)	0.8 (0.1)	1.1 (0.4)
Purpura	2.2 (0.2)	1.6 (0.1)	0.0 (0.0)
Vomiting	1.9 (1.4)	1.4 (0.9)	0.9 (0.4)
Flatulence	1.5 (0.1)	1.4 (0.3)	0.0 (0.0)
Pruritus	1.3 (0.8)	0.3 (0.1)	0.0 (0.0)
Dizziness	1.1 (0.4)	0.5 (0.4)	0.0 (0.0)
Anorexia	1.0 (0.4)	0.5 (0.3)	0.0 (0.0)
Abnormal Liver Function test	1.0 (0.7)	0.3 (0.3)	0.0 (0.0)

Incidence of discontinuation, regardless of relationship therapy, is shown in parentheses

Neutropenia/Thrombocytopenia See Warnings. **Gastrointestinal** TICLID therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and typically are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. **Hemorrhagic** TICLID has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding and perioperative bleeding. Intracerebral bleeding was rare in clinical trials with TICLID, with an incidence no greater than that seen with comparator agents. (Ticlopidine 0.5%, aspirin 0.6%, placebo 0.75%.) **Rash** Ticlopidine has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean onset time of 11 days. If drug is discontinued, recovery occurs within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of severe rashes. **Less Frequent Adverse Reactions (Probably Related)** Clinical adverse experiences occurring in 0.5 to 1.0 percent of patients in the controlled trials include: Digestive System: GI fullness. Skin and Appendages: urticaria. Nervous System: headache. Body as a Whole: asthenia, pain. Hemostatic System: epistaxis. Special Senses: tinnitus. In addition, rarer, relatively serious events have also been reported, mainly from foreign post marketing experience: Pancytopenia, hemolytic anemia with reticulocytosis, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, cholestatic jaundice, nephrotic syndrome, myositis, hyponatremia, immune thrombocytopenia and thrombocytopenic thrombotic purpura (TTP). **OVERDOSAGE** One case of deliberate overdosage with TICLID has been reported by foreign postmarketing surveillance program. A 38 year old male took a single 6000 mg dose of TICLID (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Single oral doses of ticlopidine at 1600 mg/kg and 500 mg/kg were lethal to rats and mice, respectively. Symptoms of acute toxicity were GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and abnormal gait. **DOSAGE AND ADMINISTRATION** The recommended dose of TICLID is 250 mg BID taken with food. Other doses have not been studied in controlled trials for these indications.

SYNTEX

SYNTEX LABORATORIES, INC.
PALO ALTO, CA 94304

U.S. Patent Nos. 4,051,141; 4,591,592
02-0431-00-00 NOVEMBER 1991
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POST HERPETIC NEURALGIA

There Are Many Words To Describe The Pain.

STABBING
PENETRATING
SHARP
JABBING
SHOOTING
UNBEARABLE
PIERCING
GRIPPING
SEARING

And One For Treating It.

Topical
Zostrix®
(Capsaicin 0.025% w/w) Cream

When patients describe the "hurt" of postherpetic neuralgia (PHN), they use a wide range of words to describe a pain that is often intractable and difficult to treat. Zostrix® (Capsaicin 0.025% w/w) Cream provides an effective topical treatment that alleviates intense pain in most PHN patients.

Topical Zostrix Works Where It Hurts

Zostrix®

(Capsaicin 0.025% w/w) Cream

Topical Analgesic

TARGETED ACTION

Acts on sensory nerves at site of application by selectively depleting substance P, a chemomediator of pain impulses along neuropathways.

EFFECTIVE

Alleviates the intense pain associated with postherpetic neuralgia in most patients. May also benefit patients when added to existing systemic drug regimens.

SAFE

No known interactions with systemic medications commonly prescribed for geriatric patients.

Topical Zostrix Works Where It Hurts

DESCRIPTION

Zostrix Cream contains capsaicin, 0.025% w/w, in an emollient base containing benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, polyoxyethylene stearate blend, purified water, sorbitol solution and white petrolatum. Capsaicin is a naturally occurring substance derived from plants of the Solanaceae family with the chemical name trans-8-methyl-N-vanillyl-6-nonenamide. Capsaicin is a white crystalline powder with a molecular weight of 305.4. It is practically insoluble in water but very soluble in alcohol, ether and chloroform.

ACTION

Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemomediator of pain impulses from the periphery to the central nervous system. In addition, substance P has been shown to be released into joint tissues and activate inflammatory mediators involved with the pathogenesis of rheumatoid arthritis.

INDICATION

Zostrix is indicated for the temporary relief of peripheral neuralgias such as the pain following shingles (herpes zoster). Zostrix is also indicated for the temporary relief of the pain associated with rheumatoid arthritis and osteoarthritis.

WARNINGS

FOR EXTERNAL USE ONLY. Avoid contact with eyes and broken or irritated skin. Do not bandage tightly. If condition worsens, or does not improve after 28 days, discontinue use of this product and consult your physician. **Keep this and all drugs out of the reach of children.** In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

DIRECTIONS

Adults and children 2 years of age and older: Apply Zostrix to affected area 3 to 4 times daily. Transient burning may occur upon application, but usually disappears in 72 hours. Application schedules of less than 3 to 4 times a day may not provide optimum pain relief and the burning sensation may persist. **Wash hands immediately after applying Zostrix.**

HOW SUPPLIED

1.5 oz tube (NDC 52761-552-45)
3.0 oz tube (NDC 52761-552-85)

Store at room temperature.
U.S. Patent Nos. 4486450 and 5536404

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Calendar of Meetings

July

5-10 11th European Congress on Sleep Research, University of Helsinki (Finland). Contact 11th European Congress on Sleep Research 1992, c/o The Finnish Medical Society Duodecim, Kirsi Saarelma, Kalevankatu 11 A, SF-00100 Helsinki, Finland.

12-17 Third International Conference on Alzheimer's Disease and Related Disorders, Padua, Italy. Contact Congress Department, Galleria Zabarella 4, 35121 Padova, Italy.

14-17 Fourth International Conference, Neuroscience of Human Immunodeficiency Virus Infection, Amsterdam, the Netherlands. Contact Conference Secretariat, Bureau PAOG Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, the Netherlands.

July 30-August 2 Tenth Annual Symposium on Medical Problems of Musicians and Dancers, The Wheeler Opera House, Aspen, Colo. Contact The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Ave, Room TT-31, Cleveland, OH 44195-5241; (216) 444-5696: (800) 762-8173.

September

22-25 First International Symposium on Brain Death, Havana, Cuba. Contact First Symposium on Brain Death, Palacio de las Convenciones, Apartado 16046, Havana, Cuba.

23-25 13th Annual Traumatic Head Injury Conference, Royal Sonesta Hotel, Boston, Mass. Contact Braintree Hospital, Public Relations Department, 250 Pond St, Braintree, MA 02184; (800) 333-2561, extension 2300.

October

15-17 "Neuro-Oncology: Recent Advances in Diagnosis and Treatment," New York, NY. Contact Mary Callaway, Neurology Department, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, Box 52, New York, NY 10021; (212) 639-6754.

18-21 117th Meeting of the American Neurological Association, Toronto, Ontario. Contact American Neurological Association, 2221 University Avenue SE, Suite 350, Minneapolis, MN 55414; (612) 378-3290.

Neuroanesthesia: Handbook of Clinical and Physiologic Essentials

Ed 2, edited by Philippa Newfield and James E. Cottrell, 458 pp, with illus, $50, Boston, Mass, Little, Brown & Co Inc, 1991.

This book, published in a portable, soft-cover format, is a concise treatment of the current practice of neuroanesthesia. The first edition, published in 1983, was the earliest entry in this category and, as such, filled a void. The second edition is, at a minimum, an update and, in some areas, an expansion of some tersely treated subjects of the first edition. The result is a compact, yet thorough, treatment of clinically relevant topics and guidelines for the delivery of perioperative anesthetic care of neurosurgical patients.

The book contains chapters provided by over 30 contributors who discuss material derived primarily from anesthesiology, although some contributors represent the disciplines of neurosurgery and neuroradiology. Notable contributors from neuroanesthesia include, among others, James Cottrell, Elizabeth Frost, Betty Grundy, Jane Matjesko, and Donald Prough. All 17 chapters of this book are categorized into one of three broad sections: "General Considerations," "Intensive Care," and "Anesthetic Management." Under "General Considerations" are chapters addressing physiology and metabolism of the central nervous system and the effects of anesthesia on the same, electrophysiologic monitoring, and cerebral damage and protection. The section on "Intensive Care" discusses pulmonary and cardiovascular management. "Anesthetic Management" is appropriately the largest section and contains chapters that consider a complete spectrum of neuroanesthetic topics, ranging from intracranial aneurysms to neuroradiologic procedures. Some areas that have been significantly expanded deal with pharmacologic brain protection, anesthetic management of the patient with spinal cord injury, treatment of vasospasm following subarachnoid hemorrhage, and pediatric neuroanesthesia.

Individual chapters are presented in an outline form that begins with a general background. This is followed by subsections that address salient topics in the preoperative and postoperative periods as well as those in the intraoperative period. The structure of the subsections provides specific background, clinical considerations, and a practical approach to management. This format provides an efficient, intelligible vehicle for understanding the clinical issues and their underlying scientific principles, followed by clear guidelines on suggested clinical care. This organization, along with the liberal use of boldfacing to highlight key terms and phrases, makes this text function well as a quick reference. Finally, every chapter is concluded by a sizeable list of current references.

Overall, *Neuroanesthesia* is a comprehensive, yet concise, treatment of the anesthetic management of neurosurgical patients in the perioperative period. As such, it is recommended highly as a practical reference to anesthesia providers who provide neuroanesthesia intermittently, to trainees in anesthesiology, and to subspecialists who may require a quick refresher. Furthermore, its treatment of clinical care outside the operating room makes it a useful handbook in caring for neurosurgical patients in the intensive care setting.

KEVIN J. GINGRICH, MD
Rochester, NY

Drug Therapy for Headache

Edited by R. Michael Gallagher, 312 pp, with illus, $79.95, New York, NY, Marcel Dekker Inc, 1991.

This small book contains chapters on prophylactic and abortive treatment of migraine attacks and also on treatment of tension-type, cluster, and "mixed" headache. Also included are chapters on use of analgesics, on headache classification and pathophysiology, and on other syndromes of head pain. The brevity of the book demands comparatively brief coverage of most of these subjects, particularly those not dealing with medication, but the statements in general are up-to-date and accurate. The provision of details of medication dosage and side effects, much of it given in table form, will be of use to the busy clinician. The chapters on migraine treatment and on drug interactions are particularly detailed and helpful.

The statements in *Drug Therapy for Headache* are, in general, fair minded and representative of the consensus but often do not mention the uncertainty and controversy on many subjects. Many of the subjects covered are discussed in much greater detail in the many other, more lengthy books on headache, but this brief book should find its particular place in the areas indicated by its title. One minor criticism: although this book covers more than drug treatment of headache, it does not include any thoughtful discussion of the place of simple explanation and reassurance so important to many of these patients.

DEWEY K. ZIEGLER, MD
Kansas City, Kan

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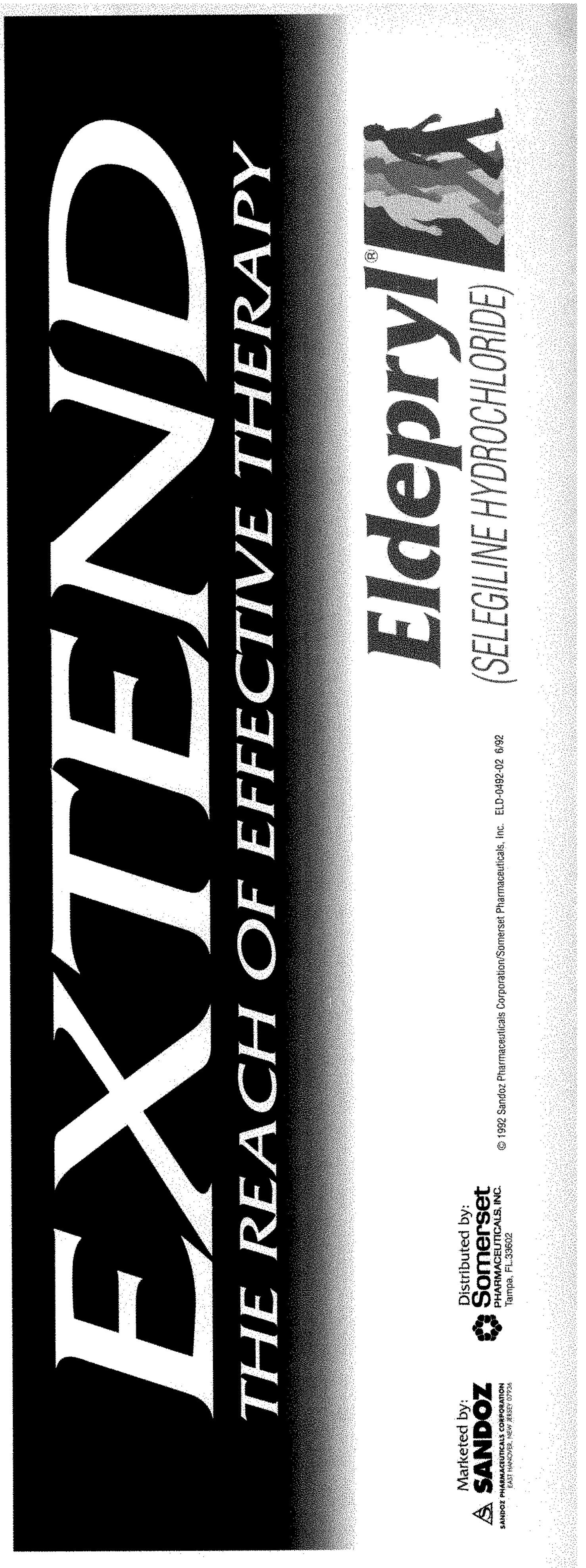

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Eldepryl®

(SELEGILINE HYDROCHLORIDE) Tablets

BRIEF SUMMARY: Please see package insert for full prescribing information.

CLINICAL PHARMACOLOGY:

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

INDICATIONS AND USAGE:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is contraindicated in patients with a known hypersensitivity to this drug.

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is contraindicated for use with meperidine (DEMEROL and other trade names). This contraindication is often extended to other opioids (see Drug Interactions).

WARNINGS:

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Definitive clinical data on the concomitant use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) and fluoxetine hydrochloride (PROZAC) is not available. Death has been reported to occur following the initiation of therapy with nonselective MAOI's (NARDIL, PARNATE) shortly after discontinuation of fluoxetine. To date, this reaction has not been reported with ELDEPRYL® (SELEGILINE HYDROCHLORIDE), however, since the mechanism of this reaction is not fully understood it seems prudent, in general, to avoid this combination. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately 5 half-lives) should elapse between discontinuation of fluoxetine and initiation of MAOI therapy. Based on experience with the combined use of MAOI's and tricyclic antidepressants, at least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with fluoxetine.

PRECAUTIONS:

General: Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients: Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline have not been reported, documented experience is limited. Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests: No specific laboratory tests are deemed essential for the management of patients on ELDEPRYL® (SELEGILINE HYDROCHLORIDE). Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions: The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in a man receiving selegiline and meperidine, as well as other medications. Symptoms resolved over days when the combination was discontinued. This case is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination. While it cannot be said definitively that all of these reactions were caused by this combination, they are all compatible with this well recognized interaction. No other interactions attributed to the combined use of selegiline and other drugs have been reported. However, because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. (See WARNINGS and PRECAUTIONS.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies have not been performed to date to evaluate the carcinogenic potential of selegiline hydrochloride.

Pregnancy: *Pregnancy Category C.* Insufficient animal reproduction studies have been done with selegiline to conclude that selegiline poses no teratogenic risk. However, one rat study carried out at doses as much as 180 fold the recommended human dose revealed no evidence of a teratogenic effect. It is not known whether selegiline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Selegiline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use: The effects of selegiline hydrochloride in children have not been evaluated.

ADVERSE REACTIONS:

Introduction: The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have been also reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness and weight loss.

Experience with ELDEPRYL® (SELEGILINE HYDROCHLORIDE) obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

CENTRAL NERVOUS SYSTEM:

Motor/Coordination/Extrapyramidal: increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric: hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

AUTONOMIC NERVOUS SYSTEM: Dry mouth, blurred vision, sexual dysfunction.

CARDIOVASCULAR: Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

GASTROINTESTINAL: Nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

GENITOURINARY/GYNECOLOGIC/ENDOCRINE: Slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

SKIN AND APPENDAGES: Increased sweating, diaphoresis, facial hair, hair loss, hemotoma, rash, photosensitivity.

MISCELLANEOUS: Asthma, diplopia, shortness of breath, speech affected.

POSTMARKETING REPORTS: The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE).

CNS: Seizure in dialyzed chronic renal failure patient on concomitant medications.

*indicates events reported only at doses greater than 10 mg/day.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N = 49	placebo N = 50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

OVERDOSAGE:

Selegiline: No specific information is available about clinically significant overdoses with ELDEPRYL® (SELEGILINE HYDROCHLORIDE). However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g., tranylcypromine (PARNATE), isocarboxazide (MARPLAN), and phenelzine (NARDIL)].

Overdose with Non-Selective MAO Inhibition: NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions for Overdose

NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physician's Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

[Literature issued December, 1991 011-25-P-105]

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LETTERS TO THE EDITOR

Biologically Significant Serum Vitamin B_{12} Deficiency in Multiple Sclerosis Inadequately Documented

To the Editor.—The recent article by Reynolds et al[1] on potential association of vitamin B_{12} "deficiency" and multiple sclerosis (MS) is of considerable interest to patients with MS and physicians involved in their care. The significance of this observation, however, remains unclear because convincing evidence of a vitamin B_{12} *deficiency* in patients with MS was not documented by the authors. Although the serum vitamin B_{12} assay is an extremely sensitive test for a vitamin B_{12} deficiency, it lacks specificity. It has been established that many patients with low serum B_{12} levels do not have a documentable cobalamin deficiency state. The currently available confirmatory tests for biologically significant vitamin B_{12} deficiency include determination of serum methylmalonate and homocysteine levels, which have been shown to be elevated in the vast majority of vitamin B_{12}–deficient patients with objective hematologic or neuropsychiatric changes attributable to the deficiency.[2-4] These metabolites accumulate in the serum of patients with vitamin B_{12} deficiency since cobalamins are required as cofactors for completion of the following two enzyme reactions: (1) methylmalonyl-CoA mutase, ie,

$$\text{Methylmalonyl-CoA} \rightarrow \text{Succinyl-CoA}$$

and (2) methionine synthase, ie,

$$\text{Homocysteine} + \text{Methyltetrahydrofolate} \rightarrow \text{Methionine} + \text{Tetrahydrofolate}$$

It is important to recognize that the methionine synthase reaction listed above requires methlytetrahydrofolate in addition to cobalamin. Consequently, serum homocysteine levels may also rise in folate deficiency. Patients with low serum vitamin B_{12} levels should be further screened for elevations of serum methylmalonate and homocysteine levels. Elevations of one or both of these metabolites would indicate a true state of biologically significant cobalamin deficiency, as opposed to a depletion of cobalamin stores or decreased level of transcobalamin 1, the major plasma-binding protein for vitamin B_{12}. To judge the appropriateness of vitamin B_{12} therapy, it is necessary to demonstrate a lowering of mean red blood cell volume and/or improvement of neuropsychiatric abnormalities presumed due to cobalamin deficiency when vitamin B_{12} is administered. In the case of cobalamin-deficient patients with neurologic, but not hematologic, complications, who may have a coexistent disorder such as MS, judging the efficacy of therapy may be more difficult. However, a lowering of abnormally elevated levels of serum metabolites in response to vitamin B_{12} therapy provides clear-cut evidence of an underlying deficiency state and justifies continuation of vitamin B_{12} injection for life. Until adequate documentation of a functional vitamin B_{12} deficiency is established in patients with clinically definite MS,[5] it will be difficult to know how to interpret the results of the screening tests reported by Reynolds et al. The lack of neurologic or hematologic response to vitamin B_{12} replacement reported by the authors in the only two patients followed up while they were receiving vitamin B_{12} therapy suggests that the functional vitamin B_{12} deficiency state did not, in fact, exist despite the low serum vitamin B_{12} levels recorded on screening tests.

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In Reply.—We thank Goodkin and colleagues for their interest in our article[1] on 10 patients with multiple sclerosis (MS) associated with vitamin B_{12} deficiency, and we agree with their view that the serum vitamin B_{12} assay may be an unreliable guide to a vitamin B_{12} deficiency state. Indeed, not only may some patients with a low serum vitamin B_{12} level not have a vitamin B_{12} deficiency but others with vitamin B_{12} levels above 200 pg/mL may be severely deficient.[2] For example, we have studied one patient with a high serum vitamin B_{12} level (greater than 2000 pg/mL) who had subacute combined degeneration related to a severe vitamin B_{12} deficiency state, as reflected in a megaloblastic anemia, low red blood cell vitamin B_{12} level, high plasma homocysteine level, and hematologic and neurologic response to vitamin B_{12} treatment.[3]

Goodkin and colleagues suggest that our patients with MS may not have been vitamin B_{12} deficient, because we relied on the serum vitamin B_{12} assay and did not include serum methylmalonate or homocysteine. This overlooks the fact that eight of our 10 patients were macrocytic, five out of six examined had megaloblastic bone marrows, and all six examined patients had low red blood cell vitamin B_{12} levels. The evidence for vitamin B_{12} deficiency in our patients was, therefore, substantial. Serum methylmalonate and homocysteine assays were not available either to ourselves or to the several neurologists who first saw and often treated these patients in the early and middle 1980s, before referring them to us.

We refrained from commenting on the neurologic response to treatment in most of our cases, partly because of the short or variable length of follow-up by several different neurologists and partly because such open neurologic observations in patients with MS are notoriously unreliable. We drew attention to the persisting macrocytosis in cases 1 and 2 on standard vitamin B_{12} therapy (monthly injections of 1000 μg of hydroxocobalamin), because we believe that it is further evidence of a possible disorder of vitamin B_{12} binding or transport in some of our patients. Our impression, such as it is worth, from observing these and other unpublished cases is that for neurologic benefit, and sometimes for adequate hematologic response, intensive vitamin B_{12} treatment is required.

We entirely agree that serum methylmalonate and homocysteine assays are very useful additional new tools in the assessment of both vitamin B_{12} and folate deficiency and for evaluating response to appropriate vitamin therapy. To imply, however, that the diagnosis of functional vitamin B_{12} deficiency depends on them is to imply that no one could diagnose vitamin B_{12} deficiency until recently. We have included plasma homocysteine in our systematic studies of vitamin B_{12} metabolism in patients with MS, which have been stimulated by our case reports. We[4] have shown that patients with MS as a group have significant lowering of serum vitamin B_{12} and elevation of plasma unsaturated R-binder. Furthermore, the plasma homocysteine level was significantly elevated, positively correlated with mean cell volume, and negatively correlated with serum vitamin B_{12} (T. Bottiglieri, PhD Thesis submitted to London University, 1992), thus confirming that some patients with MS are functionally vitamin B_{12} deficient.

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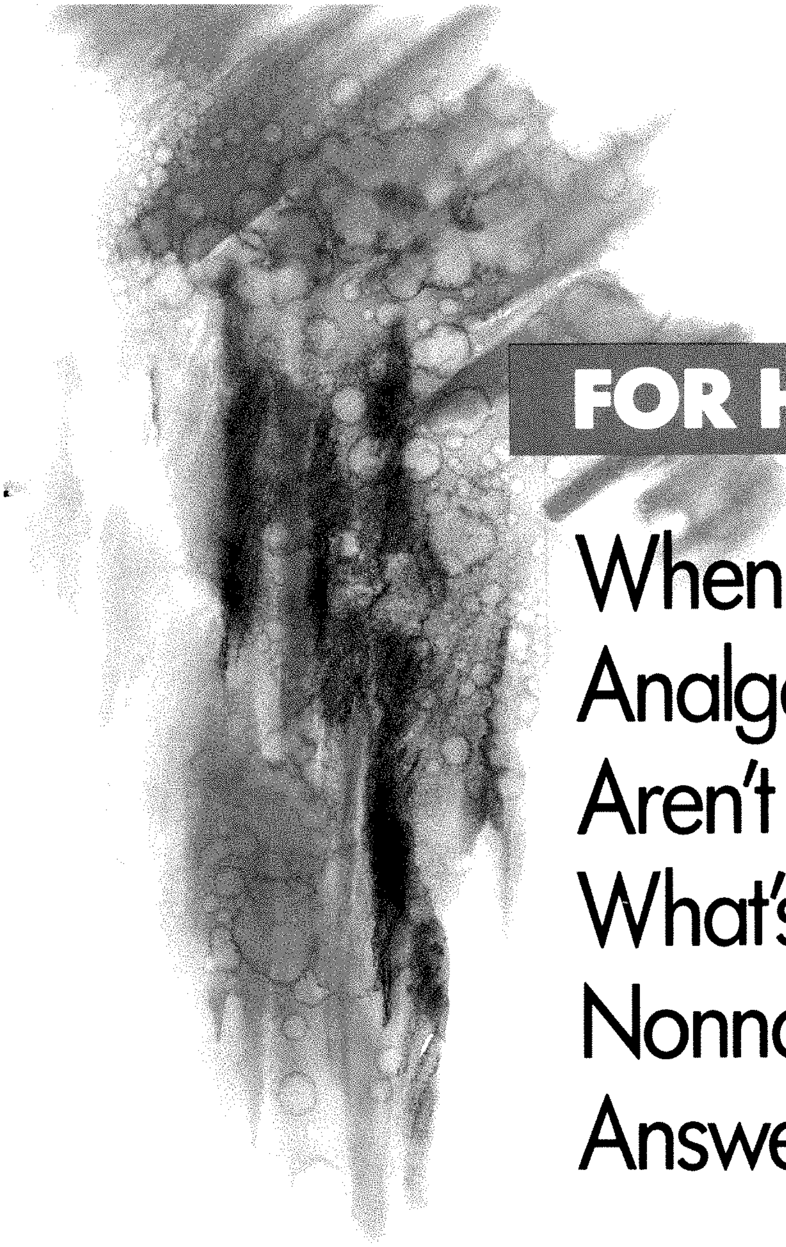
See also p 649 in the June issue.



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D.H.E. 45® is hydrogenated ergotamine as the mesylate. It is a clear, colorless, stable ampul solution containing per mL:

dihydroergotamine mesylate, USP	1mg
methanesulfonic acid/sodium hydroxide	qs to pH 3.6 ± 0.4
alcohol, USP	6.1% by vol.
glycerin, USP	15% by wt.
water for injection, USP, qs to	1 mL

ACTIONS

Dihydroergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels, and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to ergotamine, the adrenergic blocking actions are more pronounced, the vasoconstrictive actions somewhat less pronounced, and there is reduced incidence and degree of nausea and vomiting.

Onset of action occurs in 15 to 30 minutes following intramuscular administration and persists for 3-4 hours.

Repeated dosage at 1 hour intervals up to 3 hours may be required to obtain maximal effect.

INDICATIONS

As therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so-called "histaminic cephalalgia" when rapid control is desired or when other routes of administration are not feasible.

CONTRAINDICATIONS

Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy. Hypersensitivity.

ADVERSE REACTIONS

Numbness and tingling of fingers and toes, muscle pains in the extremities, weakness in the legs, precordial distress and pain, transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged use of dihydroergotamine.

DHE-0192-01 1/92

DOSAGE AND ADMINISTRATION

For vascular headache, 1 mL intramuscularly at first warning sign of headache, repeated at 1 hour intervals to a total of 3 mL. Optimal results are obtained by titrating the dose for several headaches to find the minimal effective dose for each patient and this dose should then be employed at onset of subsequent attacks. Where more rapid effect is desired, the intravenous route may be employed to a maximum of 2 mL. Total weekly dosage should not exceed 6 mL.

OVERDOSAGE

Failure to observe the upper limits of repeated parenteral dosage may result in eventual onset of the peripheral toxic signs and symptoms of ergotism. Treatment includes discontinuance of the drug, warmth, vasodilators, and good nursing care to prevent tissue damage.

HOW SUPPLIED

As a clear, colorless and stable solution in ampuls containing:

dihydroergotamine mesylate, USP	1 mg
methanesulfonic acid/sodium hydroxide	qs to pH 3.6 ± 0.4
alcohol, USP	6.1% by vol.
glycerin, USP	15% by wt.
water for injection, USP, qs to	1 mL

Ampuls, 1 mL size — boxes of 20.

To assure constant potency, protect the ampuls from light and heat. In the event the ampul solution becomes discolored, it should not be used.

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[NOVEMBER 15, 1990 DHE-Z20(BB)]

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EDITORIAL

The Value of Brain Magnetic Resonance Imaging in Multiple Sclerosis

In this issue of the ARCHIVES, Capra et al[1] report the results of biweekly magnetic resonance imaging (MRI) in 10 patients with relapsing-remitting multiple sclerosis (MS). A total of 93 gadolinium–pentetic acid (Gd-DTPA)–enhancing lesions were observed in eight patients studied during a 3-month period. Of the enhancing lesions, 88% were in the supratentorial white matter, 9% were in the brain stem or cerebellum, and 3% were in the cervical spinal cord. Seventy percent of the lesions occurred in T_2-weighted hyperintense areas already found in previous examinations. Excluding each patient's first and last scan, 64 newly enhancing lesions were observed. In 50% of the newly enhancing lesions, Gd enhancement was no longer evident on the subsequent scan, suggesting that the duration of enhancement was 4 weeks or less. Seven clinical relapses occurred in six patients, all with concurrent Gd enhancement. Gadolinium-enhancing lesions were noted in 18 MRI examinations without clinical exacerbations. One can conclude from this report that Gd-enhancing lesions frequently occur without clinical symptoms, are common in areas of previously identified T_2-weighted signal changes, and generally persist for only a few weeks. What is the potential clinical significance of this?

See also p 687.

The value of cranial MRI in documenting disseminated white matter lesions for the purpose of diagnosing MS is well established,[2-4] since periventricular high signal changes are observed in T_2-weighted images in a high frequency of patients with MS. The appearance of lesions is nonspecific, however, so that in diagnosing MS, MRI must be used in the context of a careful clinical evaluation by a physician skilled in the diagnosis of the disease. Injudicious use of MRI scanning or overinterpretation of MRI scans constitutes the leading cause of an inaccurate diagnosis of MS at the present time.

Beyond its value as a diagnostic test, what is the significance of the many MRI lesions in this disease? It is clear that most of the brain lesions are unaccompanied by evident clinical changes. For example, Jacobs et al[5] reported that only 5% of MRI lesions in patients with MS could be clearly related to clinical symptoms and that 75% of lesions were "clinically silent." As in the report by Capra et al,[1] the symptomatic lesions were observed more commonly in the brain stem or cerebellum. Kiel et al[6] reported that the correlation between the number of brain lesions and the amount of functional disability defined by the Incapacity Status Scale was not significant, and Uhlenbrock et al[7] were similarly unable to find a correlation between lesion number and Kurtzke Disability Status Scale. However, the apparent correlation between MRI lesion load and impairment severity is heavily dependent on the way impairment is measured and how it is correlated with the MRI images. Some investigators have found a correlation between the Expanded Disability Status Scale (EDSS) score[8] and the extent of MRI abnormalities.[9,10] The EDSS may be even more closely related to the amount of brain-stem and cerebellar involvement seen with MRI,[11] which is not surprising since the EDSS closely reflects motor function. Forebrain lesion load, however, is more closely related to measures of cognitive and memory impairment[12] than to motor impairment. Further evidence for the biologic significance of MRI changes is provided by the observation that the extent of lesion load, like disability status, increases with disease duration,[7,13] although this observation has not been confirmed by all investigators.[10]

A number of prospective studies of serial brain MRI scans have suggested that new lesions appear with a much higher frequency than do clinical exacerbations. Isaac et al[14] studied seven patients with relapsing-remitting MS with monthly MRI scans during a 6-month period. Eighteen new and 10 enlarging MRI lesions were observed in five patients, while only five clinical relapses were observed in three patients. Willoughby et al[15] performed brain MRI biweekly for 4 to 6 months in nine patients with relapsing-remitting MS. Six of the nine patients had development of 12 asymptomatic new lesions unaccompanied by clinical exacerbations. Serial imaging of patients with a progressive course[16] showed a significantly higher rate of new lesion accrual than did patients classified clinically as having exacerbating remitting disease, suggesting that the rate of appearance of new lesions correlates with the clinical pattern and severity of disease.

The presence of lesion enhancement following administration of gadolinium–pentetic acid/dimeglumine (gadolinium) is thought to represent "active" MS plaques.[13,17] Harris et al[18] followed six patients with relapsing-remitting MS with monthly Gd-enhanced MRI scans over a course of 8 to 11 months. While only two patients experienced clinical exacerbations during the study, numerous enhancing lesions were present in each case. The average number of Gd-enhancing lesions per scan ranged from 0.7 to 6.2. Neither the frequency of clinical exacerbation nor the change in disability during the study correlated with the frequency of Gd-enhancing lesion accrual, although the duration of follow-up was too short to observe clinical deterioration.

What then are the critical questions to be addressed in future studies of the role of brain MRI in MS? (1) What is the predictive value of brain MRI when a patient first presents to the physician with neurologic symptoms? Early studies[19,20] suggest that disseminated lesions on brain MRI scans predict subsequent clinical dissemination in patients with monosymptomatic presentations such as optic neuritis or transverse myelitis. A study sponsored by the National Institutes of Health is ongoing to determine the predictive value of MRI at the time of first MS symptoms (R. Grossman, MD, oral communication, October 1991). (2) Does the rate of new or enhancing lesion accrual predict the subsequent rate of clinical deterioration? The studies by Harris et al[18] and Capra et al[1] could potentially answer this question by careful follow-up of the patients to determine the extent of clinical disease progression. (3) What are the optimal techniques for quantifying lesion burden in MS? Should we be counting lesions? Should we be counting Gd-enhancing lesions? Should we be measuring plaque volume? (4) What is the optimal frequency for serial MRI scans in patients with MS? Should the practicing clinician request a follow-up MRI study to follow disease progression and guide therapy? Currently, a study sponsored by the National Institute of Neurological Disorders and Stroke is investigating these questions by following up 45 patients with frequent Gd-enhanced MRI studies as well as clinical and immunologic assessment (H. Weiner, MD, oral communication, October 1991). (5) Can we test putative therapies in MS by directing treatment at a reduction in the rate of new or newly enhancing lesion accrual? Three studies are funded by the National Multiple Sclerosis Society looking at this question (D. E. Goodkin, MD, A. Rostami, MD, and J. Cohen, MD, oral communications, December 1991). (6) Can we discern the histopathologic features from proton MRI or with spectroscopy? Can we tell active from inactive lesions? Can we define the imaging features of remyelination? Studies to date suggest that similar appearances derived from T_2-weighted spin echo sequences are observed in tissue with different pathologic features.[21] However, newer techniques may allow pathologic classification of lesions in vivo.

The article by Capra et al[1] lends additional support to the view that pathologic events in MS are more frequent and widespread than is evident by clinical symptoms and signs. One has the feeling that we are just getting an inkling of the potential value of MRI in diagnosis and treatment of patients with MS.

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Gadolinium–Pentetic Acid Magnetic Resonance Imaging in Patients With Relapsing Remitting Multiple Sclerosis

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Antonio Chiesa, MD; Roberto Gasparotti, MD

• Ten patients with relapsing-remitting multiple sclerosis have been studied by serial gadolinium–pentetic acid magnetic resonance imaging (MRI) every 14 days for 3 months. At the end of the follow-up, seven relapses occurred in six patients; no therapy was administered during the study. Ninety-three enhancing lesions were collected in eight patients. With regard to the duration of the enhancement, 32 lesions were detected in only one MRI scan and 32 were found in more MRI scans (most of the lesions occurring in two serial examinations). Four old lesions increased their size with delayed enhancement. Correlation was found between the relapses and the gadolinium–pentetic acid–enhancing areas only for one brain-stem and two cervical spinal cord lesions. Gadolinium–pentetic acid MRI provides useful information about activity of the disease that cannot be obtained clinically even if the dynamic of the lesions may be undervalued in old plaques.

(*Arch Neurol.* 1992;49:687-689)

The correlation between the clinical course and the pathologic process is notoriously poor in multiple sclerosis (MS). Magnetic resonance imaging (MRI) is a well-established technique for the assessment of the MS lesions[1,2] and gadolinium–pentetic acid (Gd-DTPA), a paramagnetic contrast medium, can show the increase of the blood-brain barrier (BBB) permeability, a sign of pathologic activity and plaque development.[3-6] Gadolinium–pentetic acid MRI should be a useful tool in monitoring disease activity.[7] Therefore, we have studied the course of the illness in patients with relapsing-remitting MS, who are not receiving therapy, by means of Gd-DTPA MRI.

See editorial comment on p 685.

PATIENTS AND METHODS

Patient Selection

Ten patients with clinically definite MS according to the criteria of Poser et al[8] were studied. Clinical selection criteria were as follows: no immunosuppressants before the study, no psychosis, no pregnancy, a score of less than 4 on the Expanded Disability Status Scale,[9] a clinical relapsing-remitting course, and no evidence of secondary progression. The patients, three men and seven women, accepted to receive no steroid therapy in case of relapse during the study. Their ages were between 23 and 46 years (mean age, 30 years), with duration of illness between 2 and 10 years (mean duration, 6 years). At the beginning of the follow-up, Expanded Disability Status Scale scores ranged from 1 to 3 (mean, 2). All patients had an MRI without Gd-DTPA before the study.

Patient Evaluation

The patients underwent brain and spinal cord MRI without and with the injection of Gd-DTPA, every 14 days, for 3 months. At the end of every MRI examination, clinical examinations were used to evaluate symptoms and signs of neurologic dysfunction. The patients and the examining physician were "blinded" to the results of MRI. The occurrence of a symptom or sign of neurologic dysfunction lasting more than 24 hours was considered a relapse.

MRI Scans

Magnetic resonance imaging was performed with a 1.5-T superconductor unit (Magnetom, Siemens, Erlangen, Germany). Spin-echo images of the brain were acquired using a head coil, 256×256 matrix, 20-cm field of view, and 5-mm-thick sections. The in-plane spatial resolution was 0.75 mm. The T_1-weighted (650/15/2 [repetition time/echo time/excitations]) and T_2 axial images (2000/15 to70/1 [repetition time/echo time]) with 20% interslice gap were obtained with a complete coverage of the brain. In all patients, T_1-weighted images were also obtained after intravenous administration of gadolinium–pentetic acid (Shering, Berlin, Germany) 0.2 mL/kg of body weight (0.1 mmol/kg). The contrast media was administered without changing the patient's position. Contrast-enhanced T_1-weighted images of the brain were collected 10 minutes after the injection. A mild T_2 weighting was preferred for a better distinction of small periventricular demyelinating lesions. The spinal cord examination was based on T_1-weighted sagittal spin-echo images (500/15 repetition time in milliseconds/echo time in milliseconds) that were acquired after gadolinium–pentetic acid injection. Contiguous 3-mm-thick slices were obtained separately for the cervical and dorsal segments with a surface receiver coil. Serial examinations were performed with an accurate repositioning of the patient's head to obtain comparable sections at the same anatomic location. The position of the head was determined with the help of a laser

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Findings on the Neuroradiologic and Neurologic Examinations*

	Neuroradiologic Examination						Neurologic Examination											
	MRI, No. of Lesions†						Symptoms						Signs					
	Sequence						Sequence‡											
Patient No.	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	20	15	16	21	20	15	...	...	LLW, H	P	P	P	...	...	LLW, H	H	...	...
2	0	0	0	0	0	0	...	...	...	...	...	...	...	...	...	...	...	...
3	0	1	1	1	2	2	...	...	...	...	...	RLW	...	...	...	...	...	...
4	1	0	0	1	0	1	...	...	...	...	...	...	...	...	...	...	...	...
5	1	1	1	1	0	0	...	LLW	LLW	LLW	...	...	...	LLW	LLW	LLW	...	...
6	1	1	1	3	7	4	...	...	...	...	...	...	...	...	...	...	...	...
7	12	8	6	2	1	1	...	...	LLW	LLW	LLW	LLW	...	...	LLW	LLW	LLW	LLW
8	0	0	1	0	0	0	...	...	DIP	...	...	...	...	...	INO	...	...	...
9	0	0	0	0	0	0	...	...	...	...	...	...	...	...	...	...	...	...
10	0	0	0	0	1	1	...	...	...	...	PT	...	...	...	...	...	...	H

*LLW indicates left leg weakness; P, truncal and legs paresthesia; H, truncal and legs hypoesthesia; RLW, right leg weakness; DIP, diplopia; INO, internuclear ophthalmoparesis; PT, paresthesias of the tongue; and MRI, magnetic resonance imaging.

†Number of gadolinium–pentetic acid lesions in each MRI examination.

‡Sequence indicates the sequence number of the examination.

light. A sagittal midline section, on which a grid with vertical and horizontal numbered lines was superimposed, was taken as a reference image for a precise calculation of the correct head position to ensure anatomic correspondence of the slices in subsequent examinations. The MRI sequences were obtained before and after a bolus of gadolinium–pentetic acid, which was given to the patient, who was still in the scanner, over 2 minutes. The enhanced images were collected 10 minutes after the injection of gadolinium–pentetic acid. The largest diameter of the Gd-DTPA–enhancing lesions was measured directly on the monitor using the conversion scale of the equipment.

RESULTS

Patient Evaluations

Sixty clinical examinations were performed. Seven relapses occurred in six patients: symptoms and results of neurologic examinations were concordant in four patients. In three patients, relapses corresponded to Gd-DTPA–enhancing lesions: paresthesia of the trunk and legs (patient 1) and left leg weakness (patient 7) occurred concomitantly with two lesions in the cervical spinal cord, and diplopia (patient 8) occurred with one lesion in the brain stem. No relapse occurred without concomitant Gd-DTPA–enhanced areas but Gd-DTPA enhancements were found without signs or symptoms of neurologic dysfunction in the scans from 18 MRI examinations (Table). At the end of the follow-up, the Expanded Disability Status Scale score of the patients did not change.

T_2-Weighted MRI Characteristics

One hundred forty-six hyperintense areas (123 supratentorial, 22 infratentorial, and one in the cervical spinal cord) were identified in T_2-weighted images in the first MRI examination. Periventricular confluence of the lesions was found in seven patients. One hundred fifty-four hyperintense areas (130 supratentorial, 22 infratentorial, and two in the cervical spinal cord) were identified in T_2-weighted scans in the last MRI examination. No correlation was found between the disability and MRI T_2-weighted lesions at the beginning of the study.

T_1-Weighted Gd-DTPA MRI Characteristics

Sixty Gd-DTPA MRI scans of the brain and of the spinal cord were performed. Ninety-three T_1-weighted Gd-DTPA–enhanced areas were found in eight patients during the study: 82 lesions in the supratentorial areas, eight in the brain stem and cerebellum, and three in the cervical spinal cord. No Gd-DTPA–enhanced areas were found in two patients. Sixty-five supratentorial Gd-DTPA enhancements occurred in T_2-weighted hyperintense areas already found in previous examinations (Gd-DTPA enhancement of old lesions) and most of them were located in the periventricular confluence. Seventeen supratentorial enhanced areas were new lesions and they were outside the periventricular area. All brain-stem and cerebellum Gd-DTPA enhancements occurred in previously found T_2-weighted hyperintense areas. Two of the three cervical spinal cord lesions were new. To determine the duration of the enhancement, Gd-DTPA–enhancing areas in the first and last scan were not included: 32 lesions were found in only one MRI scan and 32 lesions continued to enhance for more than one examination (21 were detected in two examinations, six were detected in three examinations, and five were detected in four examinations). These 64 Gd-DTPA–enhancing areas were divided by dimension: among the 32 single-appearance lesions, 18 were less than 5 mm in diameter, 13 were more than 5 mm, and one was more than 1 cm. Among the 32 lesions appearing in more than one examination, seven lesions were less than 5 mm in diameter, 21 were more than 5 mm, and four were more than 1 cm. One Gd-DTPA enhancement in the cervical spinal cord persisted from the first to the last scan. During the follow-up, three supratentorial Gd-DTPA–enhancing areas changed their enhancement into a ring shape before disappearing. Four Gd-DTPA supratentorial enhancements were preceded by the enlargement of the corresponding T_2-weighted hyperintensity, detected in previous serial examinations. The tendency of the plaques to enhance in temporal cluster was observed in three patients.

COMMENT

In assessing the course of MS, clinical studies may be misleading as the activity of the immunopathologic process does not correlate with changes in disability.[4,10,11] Multiple sclerosis lesions may be detected by MRI and the signal abnormalities correspond to the pathologic process[1,12]; moreover, the Gd-DTPA enhancement is a reliable marker of increased BBB permeability in patients with relapsing-remitting MS.[3,7] In our study, Gd-DTPA MRI showed a continuous appearance and disappearance of BBB opening, often with unchanged results of clinical examinations. During the follow-up, the supratentorial-enhancing lesions did not correlate with the relapses. Only two of the three acute plaques of the cervical spinal cord and a brain-stem–enhancing lesion were symptomatic, although small lesions of the spinal cord could be missed by the less satisfactory MRI scanning of the spinal cord than of the brain. The absence of correlation between MRI and the clinical examination could be due to the fact that most of the Gd-DTPA–enhancing areas were located in the periventricular confluence of demyelination. The distribution of the enhancing lesions also explains the slight increase of the number of the T_2-weigthed hyperintensities at the end of the study. However, the new supratentorial lesions were not symptomatic, even when located near the cortex or in the white matter, not adjacent to the ventricles. Our results are in accord with the study of Harris et al[13] in patients with early, mild MS, except for the spinal cord that was not imaged. On the contrary, in a prospective monthly MRI study, Isaac et al[14] found a larger number of new lesions than old ones; Koopmans et al[15] and Willoughby et al[10] reported also that active lesions were more often outside the periventricular location. The results of our study might be due to the Gd-DTPA that pointed out the BBB opening in areas of plaque confluence, where a modified lesion is noticed with difficulty. The Gd-DTPA also enhanced small lesions (<5 mm in diameter) in the brain stem, cerebellum, and near the cortex, which could not be enlarged in the T_2-weighted images. With regard to the duration of the enhancement, in our study, half of the Gd-DTPA–enhancing lesions persisted for less than 14 days; most of the lesions that were less than 5 mm in diameter belong to this group. The large lesions and the cervical spinal cord ones had the longest enhancement. Moreover, in three large old lesions (>1 cm in diameter), the homogeneous enhancement changed subsequently into a "ring" shape; later on, segments of the ring faded until complete disappearance as a progressive restoration of the BBB breakdown occurred. The ring enhancement was not a consequence of intensity changes made by a different scanning interval since the Gd-DTPA MRI scans were performed at the same time after contrast injection. In our study, Gd-DTPA enhancement appeared concomitantly or before the enlargement of T_2-weighted lesions, but four old lesions, outside the border of the periventricular confluence of demyelination, increased their size in the T_2-weighted images without any Gd-DTPA enhancement in the corresponding T_1-weighted sequences. The enhancement appeared subsequently in the follow-up. In contrast from what is likely to happen in the new lesions, the enlargement of the old plaques might occur also without an active transport of Gd-DTPA through the endothelium, probably for a less active inflammation than in the new lesions (Gd-DTPA diffusion not detectable by the scanner) or for a local immune activity that does not modify the BBB; likewise, Gd-DTPA MRI could undervalue the active inflammation in the central nervous system. In our patients, the enhancement changed without concurrent appearance or disappearance of all the Gd-DTPA–enhancing lesions. The simultaneously opposite state of lesion activity and the disappearance of the enhanced segments of the ring plaques could be the sign of a modulation of the damage inside the central nervous system.

In conclusion, the Gd-DTPA MRI provides useful information about lesion activity that cannot be obtained by a clinical evaluation; this technique might be a useful indicator of the pathologic process in monitoring therapeutic trials. However, this hypothesis must be considered with caution, since the dynamic of lesions may be undervalued for a limited active transport of the Gd-DTPA in old plaques and because of the resolution of the scanner.

Fred D. Lublin, MD, gave technical assistance.

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Effect of Age on Autonomic and Cardiac Responses in a Rat Stroke Model

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• The cardiovascular system and its responses change with increasing age. This has seldom been considered in experimental models of stroke, although most strokes occur in the elderly. We studied 57 male Wistar rats in three age groups: 47 to 70 days old (juvenile), 110 to 152 days old (young adult), and 186 to 245 days old (mature adult), each group being subdivided into experimental and sham operation groups. All rats underwent occlusion or sham occlusion of the left middle cerebral artery and monitoring of the mean arterial blood pressure, heart rate, sympathetic nerve activity, plasma catecholamine levels, and electrocardiogram. Eight of the 12 rats in the oldest group died within 6 hours of the middle cerebral artery occlusion; of these, the youngest was 186 days old. The mature adult rats that died before completion of the experiment showed the highest level of sympathetic nerve activity and the only significant increase in the QT interval of the electrocardiogram. Following middle cerebral artery occlusion, sympathetic nerve activity increased in the young adult rats but most strikingly in the mature adult rats that died before the end of the 6-hour experiments. Plasma norepinephrine levels were significantly elevated at 4 and 6 hours after middle cerebral artery occlusion in the oldest group and only at 6 hours in the juvenile rats. The results of this study are consistent with impaired sympathetic and cardiovascular regulation in the mature adult rat. High sympathetic activity may represent one mechanism leading to fatal cardiac arrhythmias. Age-related impairment of sympathetic regulation may contribute to the higher mortality seen among elderly patients with stroke.

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Autonomic and cardiac complications of stroke are both common and important. Increased cardiac arrhythmias, raised plasma catecholamine levels, and cardiac damage, reflected clinically by increased creatine phosphokinase levels and pathologically by the demonstration of myocytolysis, have been reported.[1-5] Moreover, a small subgroup of patients with stroke recover from their strokes only to perish unexpectedly from sudden cardiac death.[6]

Although the majority of strokes occur in old people,[7] most experimental strokes are carried out in young animals. A number of physiological changes occur in humans with increasing age, including decreased baroreceptor sensitivity and increased plasma norepinephrine (NE) levels.[8-10] Additionally, the aged brain is more vulnerable to hypoxic or ischemic insults.[11] The possible relevance of these changes is suggested by the observation that stroke in the elderly is associated with a higher incidence of cardiac arrhythmias and a higher mortality.[12]

See also p 697.

We have established a reliable stroke model that mimics the main autonomic and cardiac findings of clinical stroke, including raised plasma catecholamine levels and myocardial damage, both in the cat[13] and the rat.[14] Since aged animals, like humans, show changed hemodynamic reflexes and altered catecholamine sensitivity,[15] our model seemed appropriate for studying the effect of age on autonomic and cardiac regulation after experimental stroke. Therefore, the present experiments compared juvenile, young adult, and mature adult rats as to the effects of stroke on arterial blood pressure, heart rate, electrocardiogram (ECG), sympathetic nerve activity, and plasma catecholamine concentration. Preliminary results have been presented in abstract form.[16]

MATERIALS AND METHODS

General Surgical Procedures

The experiments were carried out on 57 male Wistar rats. They were divided into three experimental (middle cerebral artery [MCA] occlusion) and three corresponding sham-treatment (sham MCA occlusion) groups: 47 to 70 days old (juvenile), 110 to 152 days old (young adult), and 186 to 245 days old (mature adult). The weights of the rats were 250±10.1, 458±7.3, and 591±9.5 g, respectively.

The rats were made to fast approximately 16 hours before surgery and given drinking water ad libitum. The rats were initially anesthetized with urethan, 1.5 g/kg, which was supplemented (0.5 g/kg) during the early surgical part of the experiment only.

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It was determined that an adequate level of anesthesia could be maintained for the duration of the experiment, which involved 6 additional hours of stroke or sham stroke. The right femoral artery and vein were cannulated for the measurement of arterial blood pressure and the administration of drugs, respectively. Pulsatile arterial pressure was measured using a transducer (Statham P23D, Gould Electronics, Florissant, Mo) and monitored on a polygraph (Grass model 7, Grass Instruments, Quincy, Mass). Mean arterial pressure was measured by filtering the pulse pressure with a 0.5-Hz high-frequency filter. Heart rate was determined from the pulse pressure using a tachograph (Grass 7P44, Grass Instruments) and continuously monitored on the polygraph. The trachea was cannulated and the rat breathed room air. Four blood samples for plasma catecholamine measurement were withdrawn from the cannula in the femoral artery during the course of the experiment.

To occlude the MCA, the head of the rat was placed in a Kopf stereotaxic frame (David Kopf Instruments, Tujunga, Calif). The left MCA was approached through an incision made in the skin over the frontalis muscle that extended from the corner of the eye caudally to just anterior to the ear. The frontalis muscle and the temporalis muscle were reflected anteriorly to expose a large portion of the squamosal bone. Removal of a portion of the bone, and exposure and ligation of the MCA, were done with the aid of a Zeiss operating stereomicroscope (Carl Zeiss, Oberkochen, Germany). A round burr hole (5 mm in diameter) was made in the rostral ventral part of the squamosal bone to expose the MCA. The burr hole was situated approximately 3 to 4 mm dorsal to the foramen ovale and 1 to 2 mm anterior to the point where the zygoma fuses to the squamosal bone. A small portion of the dura over the MCA was cut and retracted using the tip of a 30-gauge hypodermic needle. The MCA was dissected free from the pia-arachnoid and permanently occluded in 32 rats using either bipolar coagulation or a single proline ligature, at a point just dorsal to the rhinal fissure. This resulted in an occlusion that was proximal to the bifurcation of the MCA distributing to the frontal, parietal, and some portions of the occipital cortex.

The remaining 25 rats were sham-stroke controls. These rats were prepared as above, except that the MCA was not occluded.

Sympathetic Nerve Recordings

The branches of the right renal nerve were exposed using a retroperitoneal approach. The branch of the renal nerve that joins the prevertebral plexus at the greater splanchnic nerve or ganglion, as described by Sripairojthikoon and Wyss,[17] was isolated carefully from the renal artery, ligated, and cut distally. The nerve was placed on a bipolar stainless steel recording electrode and covered with a pool of warmed paraffin oil. Multiunit nerve activity was amplified (Neurolog NL100, Medical Systems Corp, Greenvale, NY), and the discriminated activity displayed on an oscilloscope (Tektronix 5113, Tektronix Inc, Beaverton, Ore), for observation. The discriminated activity was fed into a computer to obtain continuous-time and peristimulus-time histograms of the nerve activity. The renal nerve activity was rectified, integrated, and continuously monitored on the polygraph. At the end of the experiment, following the last blood sample and immediately before perfusion, the ganglionic blocker hexamethonium (2 mg/kg) was administered to determine a value for electrical noise in the nerve recording.

Blood Analyses

Four blood samples (0.6 mL) taken 10 minutes before and at 2, 4, and 6 hours after the occlusion or sham occlusion of the MCA were removed from the femoral artery cannula of each rat by a syringe. Saline injections were used as fluid replacement for the blood loss (approximately 10%). The blood was transferred to borosilicate glass capillary tubes that had been rinsed with an aqueous preservative solution containing glutathione (60 mg/mL) and EGTA (ethylene glycol-bis, β-aminoethyl ether, *N,N'*-tetraacetic acid) (90 mg/mL). Immediately following collection, the plasma was separated from the cells and transferred into polyvinyl culture tubes, sealed, and frozen at −80°C. Unconjugated NE and epinephrine (E) were measured in duplicate using the radioenzymatic assay CATAKIT (Upjohn, Kalamazoo, Mich) modified as previously described.[14] Assay sensitivities, calculated as the amounts of catecholamine needed to produce a sample disintegrations per minute–blank ratio of 2, were 0.04 nmol/L for NE and 0.3 pmol/L for E. The lowest sample-blank ratio in this assay was 8; thus, in every case the samples were well above the sensitivity of the assay. In addition, the pH, $P\text{CO}_2$, and bicarbonate values were measured using a blood gas analyzer (Corning 170, Ciba Corning, Corning, NY) on the initial blood samples and on the samples collected at 6 hours following MCA or sham-MCA occlusion.

ECG Monitoring

The ECG was monitored in the lead II configuration. The PR and QT intervals were measured 15 minutes before and at 1-hour intervals after the MCA or sham-MCA occlusion. The ECG was continuously monitored on the oscilloscope. The polygraph was run at a high speed to obtain records for the measurement of the ECG intervals.

Histological Procedures

The MCA-occluded rats were perfused transcardially with normal saline, which was immediately followed by a slow perfusion for about 1 hour with 150 mL of a 2% solution of 2,3,5-triphenyl-2H-tetrazolium chloride (TTC) (Mallinckrodt, Paris, Ky) in normal saline. The TTC reacts with intact mitochondrial oxidative enzyme systems on mitochondrial cristae and is reduced to form a bright red color. Following the TTC solution, the rats were perfused with 4% formaldehyde solution. In these rats, the brains were removed, and 1-mm frozen sections were cut on the microtome, with 10 sections cut at 50 μm between the 1-mm slices. The 1-mm sections were viewed with light-field optics using a Leitz Diaplan microscope (Wild Leitz, Heerbrugg, Switzerland) and the sections drawn using camera lucida attachment. The 50-μm sections were mounted on glass slides and counterstained with 0.125% thionin solution at room temperature and covered with coverglasses with DPX mounting medium (BDH Chemicals, Toronto, Ontario). All thionin-stained sections were examined with a Leitz Diaplan microscope using bright-field optics. The hearts were not available for histological examination.

Statistical Analysis

Statistical comparisons were made using analysis of variance and either Duncan's multiple range test or a paired *t* test; a *P* value of less than .05 was considered to indicate significance. Values are expressed as mean±SE.

RESULTS

Mortality

One of the most significant results occurred in the mature adult experimental group of rats. Eight (67%) of the 12 rats within this group died within 6 hours of the MCA occlusion. Seven of these deaths occurred 4 to 6 hours after the MCA occlusion, while one occurred only 1.3 hours after. This did not happen in any of the other groups, including the oldest sham-occluded rats. The mean age (208±8 days; range, 186 to 238 days) of the rats that died was not different from the age of those that survived (225±8 days; range, 208 to 245 days) 6 hours past the MCA occlusion in this age group. The oldest group of rats are analyzed as a group, and those that died are also used for separate analysis.

Baseline Changes in Cardiovascular Variables

The mean arterial pressure in the urethan-anesthetized rats before stroke did not differ with age and showed a continual decrease throughout the experiment in all

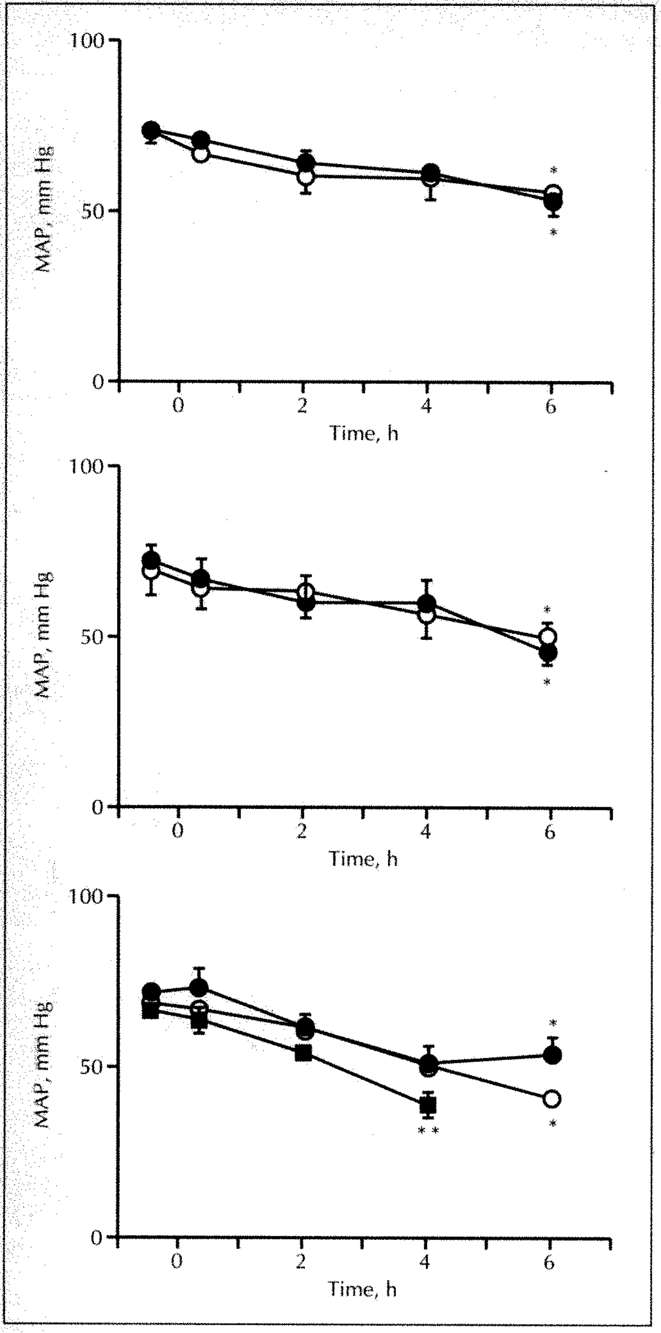

Fig 1.—*Changes in mean arterial pressure (MAP) in juvenile (top), young adult (middle), and mature adult (bottom) rats with a middle cerebral artery occlusion (MCAO) (closed circles) or a sham occlusion (SHAM) (open circles). The values were taken 30 minutes before MCAO or SHAM as well as 15 minutes and 2, 4, and 6 hours after. The third group of mature adult rats in the bottom graph (MCAO dead) (squares) were rats given MCAO that died between 4 and 6 hours after MCAO. Asterisk indicates a significant change (* $P < .05$*) within a group from before the MCAO or SHAM; double asterisks, a significant difference between the MCAO dead group and the other mature adult rats.*

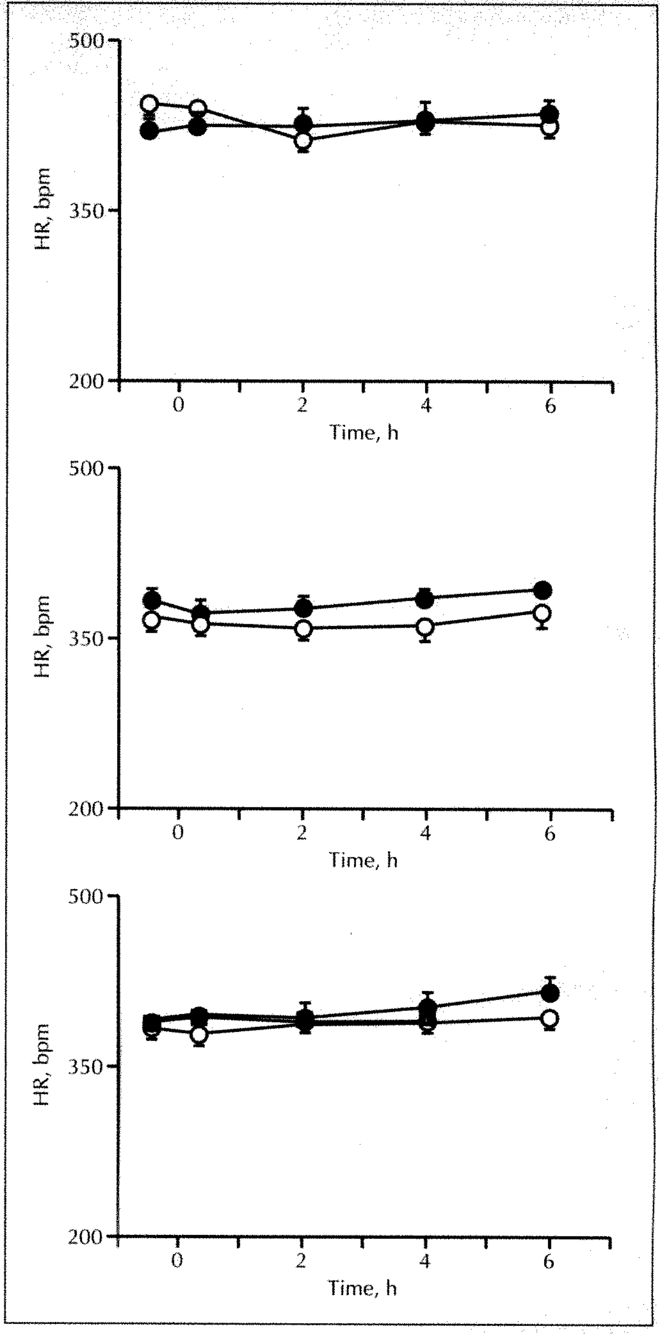

Fig 2.—*Changes in heart rate (HR) (in beats per minute [bpm]) in juvenile (top), young adult (middle), and mature adult (bottom) rats with middle cerebral artery occlusion (MCAO) (closed circles) or sham occlusion (SHAM) (open circles). The values were taken 30 minutes before MCAO or SHAM as well as 15 minutes and 2, 4, and 6 hours after. The third group of mature adult rats in the bottom graph (MCAO dead) (squares) were rats given MCAO that died between 4 and 6 hours after MCAO.*

groups. This decrease was significant at 6 hours after MCA or sham occlusion (Fig 1). Moreover, the subgroup of mature adult rats that died before the conclusion of the experiment showed a drop in mean blood pressure from baseline at 4 hours to values that were significantly lower than in the sham-treated group (Fig 1, bottom).

As expected, the heart rate before MCA or sham occlusion in the juvenile rats (432±9.5 beats per minute) was significantly higher than heart rates of the young adult (378±8.1 beats per minute) or mature adult (396±6.0 beats per minute) rats. Heart rate was not affected by MCA or sham occlusion, since it did not change throughout the duration of the experiment in any of the groups (Fig 2).

Sympathetic Changes

The initial sympathetic nerve activity was not significantly different between the juvenile (2.3±0.37 μV/s) and young adult (1.8±0.31 μV/s) groups of rats. However, the

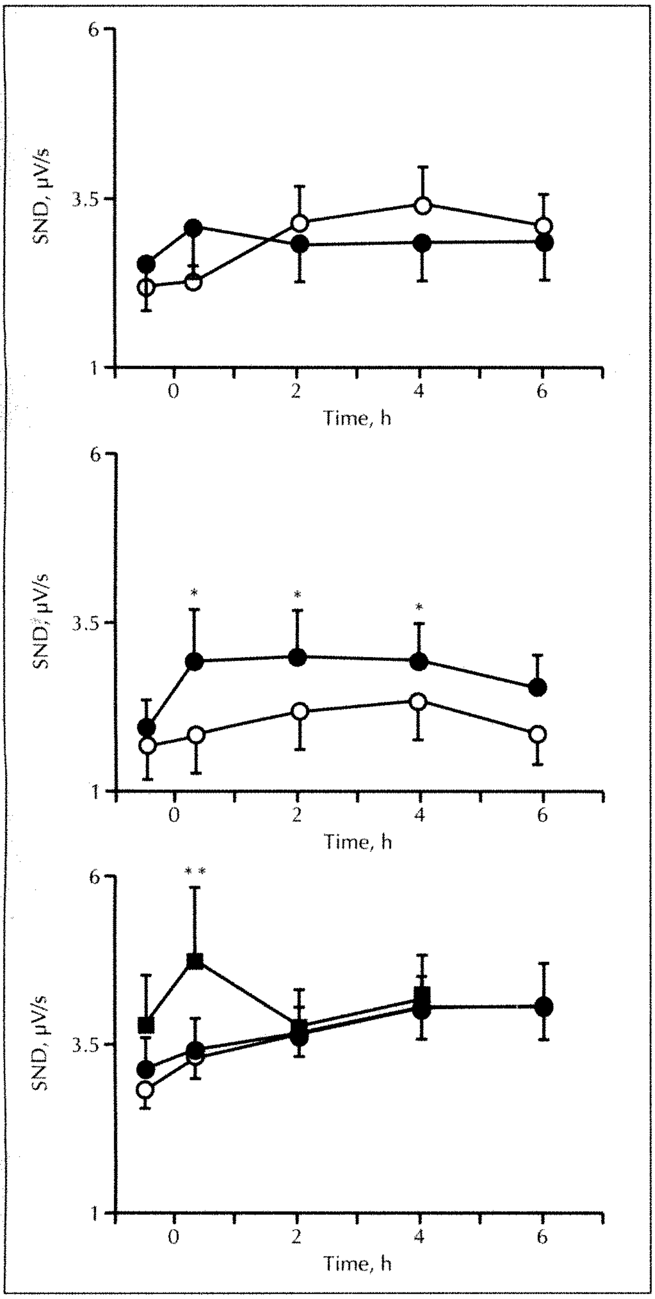

Fig 3.—*Changes in sympathetic nerve discharge (SND) in juvenile (top), young adult (middle), and mature adult (bottom) rats with middle cerebral artery occlusion (MCAO) (closed circles) or sham occlusion (SHAM) (open circles). The values were taken 30 minutes before MCAO or SHAM as well as 15 minutes and 2, 4, and 6 hours after. The third group of mature adult rats in the bottom graph (MCAO dead) (squares) were rats given MCAO that died between 4 and 6 hours after MCAO. Asterisk indicates a significant change (* P *<.05) within a group from before the MCAO or SHAM; double asterisks, a significant difference between the MCAO dead group and the other mature adult rats.*

mature adult rats had a significantly elevated (3.2±0.30 µV/s) basal sympathetic nerve activity compared with the two younger groups of rats.

There was no significant change in renal nerve activity in either the experimental or the sham-treated group of juvenile rats (Fig 3, top). In contrast, sympathetic nerve activity was significantly increased within 20 minutes after MCA occlusion and remained elevated for 4 hours after the stroke in the experimental young adult rats (Fig 3, middle). There was no difference in sympathetic nerve activity between the experimental and sham-treated groups of mature adult rats, but a significant increase in sympathetic nerve activity occurred 20 minutes after MCA occlusion in the subgroup that died before the end of the experiment (Fig 3, bottom).

Plasma Catecholamine Levels

Initial NE levels showed significant increases with increasing age, being lowest in the youngest group. The plasma concentrations were as follows: juvenile, 10.84±1.29 nmol/L; young adult, 15.96±1.33 nmol/L; and mature adult, 19.48±1.33 nmol/L. In the juvenile MCA-occluded group, NE levels were significantly increased at 6 hours after stroke compared with the initial levels (Fig 4, top). There were no significant changes in the young adult rats (Fig 4, middle). In the mature adult rats, plasma NE concentrations were significantly raised in the experimental and experimental-dead groups at 4 to 6 hours compared with initial levels (Fig 4, middle). At 6 hours, the sham-occluded rats of this oldest group also had raised NE levels compared with baseline (Fig 4, bottom).

Initial epinephrine levels also showed significant increases with increasing age of the rats, with the values as follows: juvenile, 10.63±1.50 nmol/L; young adult, 17.36±2.47 nmol/L; and mature adult, 24.94±3.25 nmol/L. However, no significant effects of sham occlusion or MCA occlusion on plasma epinephrine level occurred among any of the groups (Fig 5).

ECG Variables

The PR interval was comparable in all age groups and in experimental and sham-treated rats (Fig 6). The QT interval was not significantly different among age groups or among experimental and sham-treated rats except the experimental-dead group at 4 hours, where prolongation of QT interval presaged their demise (Fig 7). A stereotyped pattern of ECG changes preceded the death of the eight rats in the oldest group. These included an increase in the QT interval, a widening of the QRS complex, change from a flat to peaked T wave, and, eventually, complete heart block (Fig 8). Of the mature adult rats that did not die prematurely, one MCA-occluded and two sham-occluded rats also demonstrated this pattern of ECG changes.

Extent of Stroke

The region indicated by the TTC method to be included in the stroke has been previously described in detail.[14] It included portions of the lateral frontal cortex, lateral part of the primary and secondary somatosensory cortex, ventral and dorsal portions of auditory cortex, dorsal part of auditory association cortex, posterior portions of the orbitofrontal cortex, insular cortex, and anterior part of the perirhinal cortex. There were no differences in the extent of the stroke observed among the different age groups.

COMMENT

Previously, we have used the Wistar strain of rats approximately 3 months old to develop an animal model for the examination of cardiac and autonomic effects of occlusion of the MCA. In this investigation, we have subdivided these rats into three groups of approximately 2, 4, and 7 months old for examining the effects of age on the cardiac and autonomic consequences of stroke. The normal life span of the Wistar rat not reared in a disease-free en-

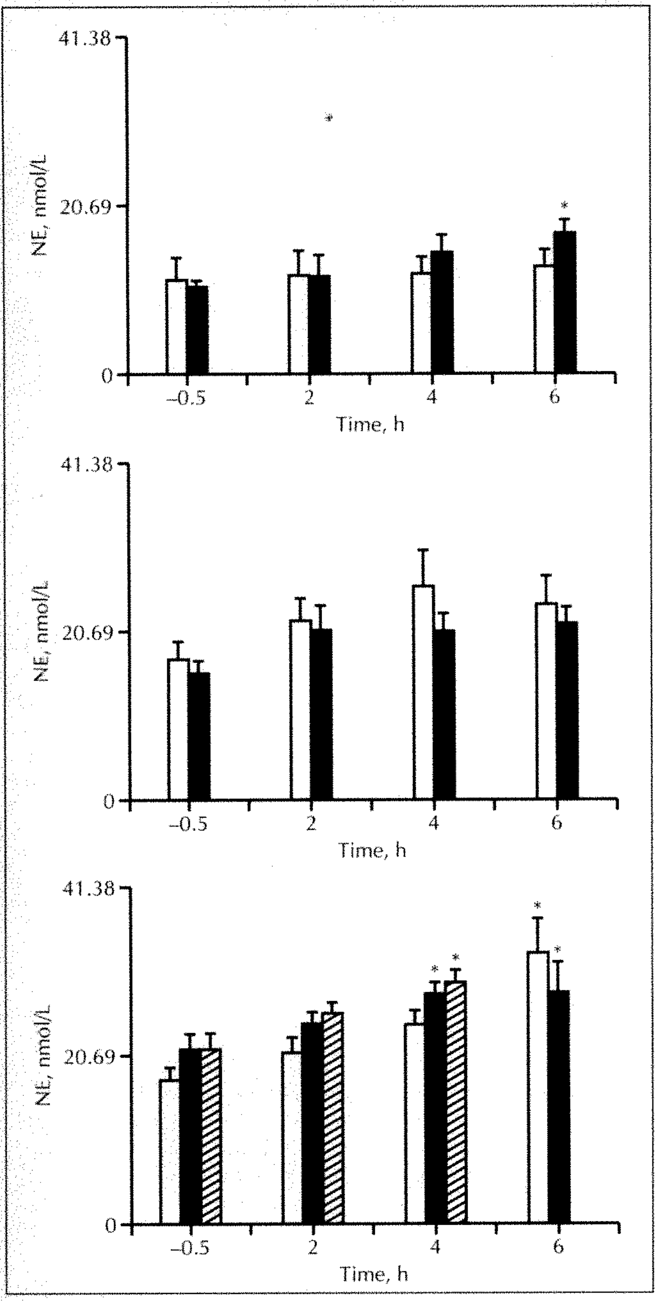

Fig 4.—*Effects of middle cerebral artery occlusion (MCAO) (closed bars) or sham occlusion (SHAM) (open bars) on plasma norepinephrine (NE) concentrations in juvenile (top), young adult (middle), and mature adult (bottom) rats. Arterial samples were taken 30 minutes before and 2, 4, and 6 hours after MCAO or SHAM. The third group of mature adult rats in the bottom graph (MCAO dead) (hatched bars) were rats given MCAO that died between 4 and 6 hours after MCAO. Asterisk indicates a significant change ($P<.05$) within a group from before the MCAO or SHAM.*

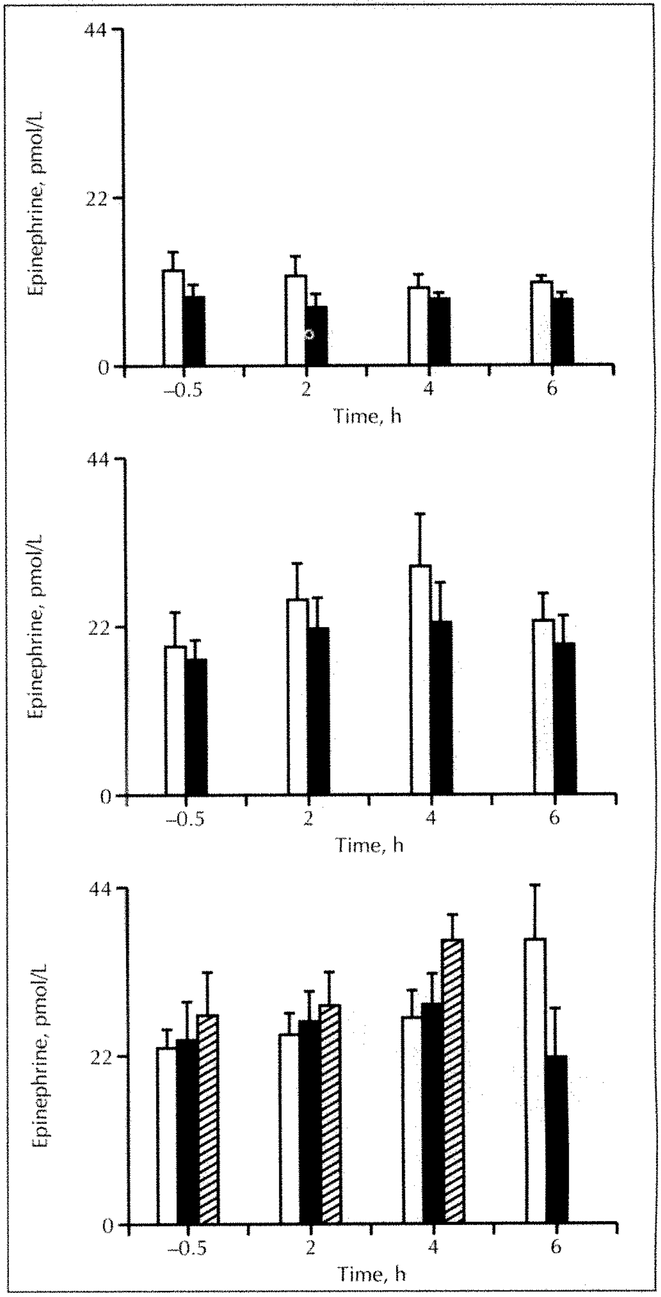

Fig 5.—*Effects of middle cerebral artery occlusion (MCAO) (closed bars) on plasma epinephrine concentrations in juvenile (top), young adult (middle), and mature adult (bottom) rats. Arterial samples were taken 30 minutes before and 2, 4, and 6 hours after MCAO or sham occlusion (SHAM) (open bars). The third group of mature adult rats in the bottom graph (MCAO dead) (hatched bars) were rats given MCAO that died between 4 and 6 hours after MCAO.*

vironment is 18 to 24 months. The results of this investigation show response patterns to MCA occlusion that are quite different among these three age groups and suggest that the autonomic and cardiac consequences are greater with increasing age.

The most striking finding was that the majority of the rats in the oldest age group that underwent MCA occlusion died before the end of the experiment. While it is possible that many events could be responsible for the demise of these rats, our comparison with control rats and experimental rats that did not die suggests that autonomic changes following MCA occlusion may play a significant role in the observed mortality. Low mean arterial pressure in the group at 4 hours revealed impairment of cardiovascular regulation and suggests that the death of these rats was due to cardiac failure. This is supported by the evidence that the decrease in mean arterial pressure corresponded to changes in the ECG that could result in a decrease in cardiac output indicative of a failing heart. The arterial pressures of juvenile, young adult, and mature adult rats were not significantly different from each other at 6 hours. Only those rats in the mature adult group for

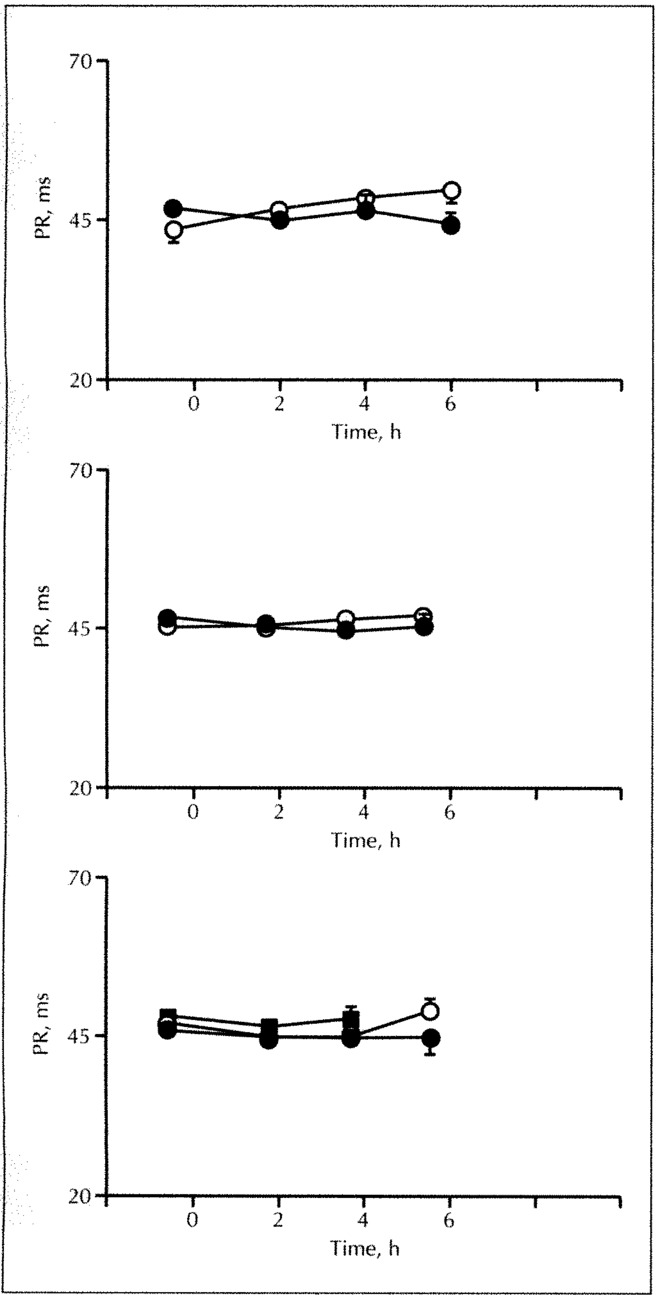

Fig 6.—*Changes in PR interval in juvenile (top), young adult (middle), and mature adult (bottom) rats with a middle cerebral artery occlusion (MCAO) (closed circles) or a sham occlusion (SHAM) (open circles). The values were taken 30 minutes before the MCAO or SHAM as well as 2, 4, and 6 hours after. The third group of mature adult rats in the bottom graph (MCAO dead) (squares) were rats given MCAO that died between 4 and 6 hours after MCAO.*

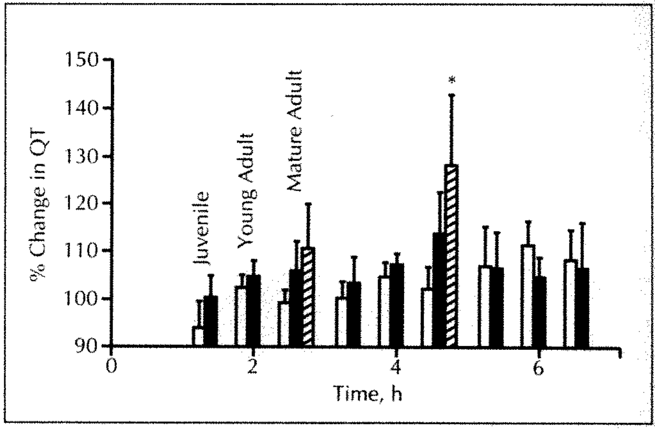

Fig 7.—*Percent change in QT interval from the initial value in juvenile, young adult, and mature adult rats with a middle cerebral artery occlusion (MCAO) (closed bars) or sham occlusion (SHAM) (open bars). The values were calculated at 2, 4, and 6 hours after the MCAO or SHAM. The third group of mature adult rats (MCAO dead) (shaded bars) were rats given MCAO that died between 4 and 6 hours after MCAO. Asterisk indicates a significant change (*$P < .05$*) within a group from the initial values before the MCAO.*

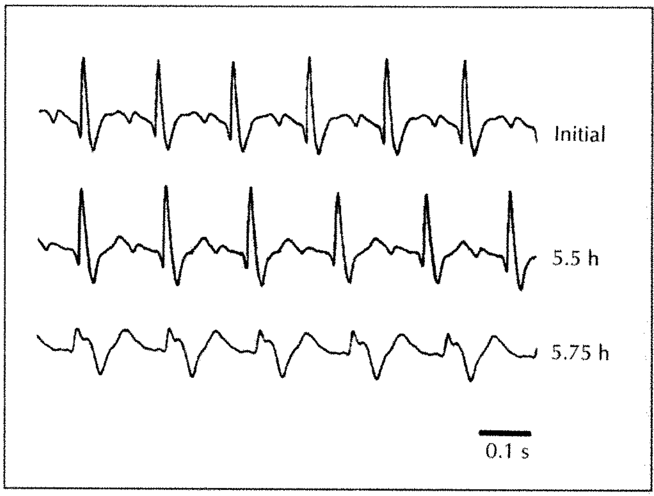

Fig 8.—*Serial electrocardiograms obtained 30 minutes before (initial) and at 5 hours 30 minutes and 5 hours 45 minutes after middle cerebral artery occlusion in a 224-day-old rat. At 5 hours 30 minutes after the MCAO, a peak in the T wave and widening of the QRS component are apparent. At 5 hours 45 minutes, complete heart block has developed, leading to the death of the rat.*

whom stroke proved lethal had significantly lower blood pressures than the sham group at 4 hours. There was no heart rate increase in the rats that died in the mature adult group despite the low mean arterial blood pressure and a large, transient increase in sympathetic nerve activity and an increase in plasma catecholamine levels from initial values. Thus, it is likely that the heart rate was maximal in urethan-anesthetized rats, even before stroke, and could not increase to compensate for the fall in mean arterial pressure. The heart rate remained remarkably steady in all age groups throughout the experiment, suggesting that changes in heart rate are not an important mechanism of compensation for drops in blood pressure under the experimental conditions of our study. These findings are in keeping with the reported decreased sensitivity of baroreceptor reflexes with aging in both humans[8,9] and experimental animals.[15,18]

It is technically difficult to make quantitative comparisons of total nerve activity when recording from peripheral nerves due to the variability that can result from the resistance between the nerve and electrode. Nevertheless, the high initial sympathetic nerve activity observed in the oldest rats was consistent with the high initial NE values with increasing age. In addition, the MCA-occluded and the sham-occluded groups for each age started at the same level of nerve activity. The sympathetic nerve activity was significantly elevated after stroke in the young adult rats, and a transient increase was observed in the oldest rats that went on to die. A direct relationship was not observed between the significant changes in renal nerve activity and plasma NE levels, although the same general trends were observed. This is due to the intermittent measure of plasma NE compared with the continuous measure of renal nerve activity, and renal nerve activity represents one small component of the whole sympathetic system.

The high initial values of plasma NE and epinephrine levels in the oldest rats are in keeping with the observation that in humans plasma catecholamine levels rise with age.[10] Elevation of plasma NE level is one of the most reliable predictors of mortality due to heart failure.[19] Catecholamines may induce arrhythmias at least in part because of catecholamine-derived oxidant injury.[20] The oldest rats had plasma catecholamine levels that were the highest before stroke and showed the greatest increases following MCA occlusion, and the oldest rats that died had the only significant increase in QT interval.

The source of the NE is likely to be neurogenic, although considerable NE may also be secreted from the adrenal medulla under some circumstances.[21] Technical limitations in our experiments prevent the measurement of cardiac sympathetic nerve activity. However, the change in renal nerve activity is considered reflective of changes in general sympathetic tone. Proportionate responses of arterial NE correlate with proportionate changes in sympathetic nerve discharge in anesthetized adrenal-demedullated rats.[22]

The high levels of plasma NE after a stroke in the mature adult group and the consequent increase in the QT interval are similar to the sequence of raised NE level, increased QT interval, and fatal arrhythmias produced in our laboratory by phasic stimulation of the insular cortex.[23] These arrhythmias were induced by selectively stimulating a sympathoexcitatory region of the insular cortex.[23] The infarcts in our present investigation included all regions of the insular cortex, likely resulting in a general disinhibition of the sympathetic nervous system, although initial transient changes may be the result of initial activation in the insular cortex with the infarct. Cardiac arrhythmias and sudden death represent significant contributors to mortality in acute stroke.[6] The higher sympathetic activity displayed in the oldest rats, as well as QT prolongation and death before the end of the experiment in some of them, suggest a possible mechanism to account for the higher mortality seen among elderly patients with acute stroke.[12]

The differences in cardiac and autonomic responses to MCA occlusion between the age groups may be the result of differences in the extent of the infarct. However, we were not able to detect differences in the volume of infarcts among the three age groups. This equivalence is supported by the investigation of Duverger and MacKenzie,[24] who demonstrated that age (3, 9, and 20 months) did not affect the volume of necrosis in the brains of Fischer 344 rats assessed 2 days after MCA occlusion.

Greater vulnerability of elderly persons to autonomic changes following stroke has another dimension: treatment. Most drug dosages have been worked out on young volunteers,[25] whereas most cardiovascular active drugs are administered to the elderly. Few studies have addressed the effect of drugs on acute cardiovascular changes in stroke in general and in the elderly in particular. Our experimental findings suggest that elderly patients with acute stroke should be considered a special group, not only in terms of proneness to cardiac and autonomic complications but also in terms of a possible altered response to their treatment with drugs.

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Asymmetry of Sympathetic Consequences of Experimental Stroke

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• Asymmetries of sympathetic regulation at the level of the inferior cervical ganglia have long been recognized. Lateralization of autonomic representation may also occur in the brain, since inactivation of the left and right hemispheres by intracarotid amobarbital produces an increase and decrease in heart rate, respectively. However, this conclusion has remained tentative, since the differential effect of lateralized brain lesions on sympathetic activity has not been studied systematically. Forty-eight urethan-anesthetized Wistar rats were divided into three groups: a group given right middle cerebral artery occlusion, one given left middle cerebral artery occlusion, and a group given sham operation. Heart rate, mean arterial blood pressure, renal sympathetic nerve discharge, and electrocardiogram were monitored throughout the 4-hour experiments. Plasma epinephrine and norepinephrine levels were measured at baseline and 1 and 4 hours after occlusion or sham occlusion. The mean arterial pressure decreased in the group given sham operation and to a lesser extent in the group given left middle cerebral artery occlusion. By contrast, mean arterial pressure did not fall in the group given right middle cerebral artery occlusion and at 4 hours was significantly higher than control values in the sham-occluded rats. Renal sympathetic nerve discharge was decreased in the sham-occluded group, increased significantly from 20 minutes to 2 hours in the group given left middle cerebral artery occlusion, and increased from about 20 minutes to the end of the experiment in the group given right middle cerebral artery occlusion. The plasma norepinephrine level was significantly elevated at 1 hour (93%) and 4 hours (44%) only in the group given right middle cerebral artery occlusion. Also, only the group given right middle cerebral artery occlusion showed a significant increase in the QT interval of the electrocardiogram, which our previous work has shown to presage fatal cardiac arrhythmias. Taken together, our data indicate that right hemisphere infarcts have greater sympathetic consequences than left hemisphere infarcts. This finding suggests lateralization of autonomic function and thus is of possible relevance to clinical stroke.

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Lateralization of sympathetic function has been clearly established at the level of the inferior cervical ganglion but remains largely undocumented at the level of the brain. The sympathetic innervation of the heart is asymmetric,[1] with the result that stimulation of the left stellate ganglion has greater arrhythmogenic effect than stimulation of the right stellate ganglion.[2] Right-left hemispheric asymmetry for heart rate has been suggested, since left hemisphere inactivation with intracarotid amobarbital increases heart rate and right hemisphere inactivation causes bradycardia.[3-5] However, we are unaware of any systematic study of cortical sympathetic asymmetries. Sympathetic activity is increased after stroke, as suggested by raised plasma catecholamine levels, elevated serum cardiac enzyme values, and increased incidence of arrhythmias and of myocytolysis.[6-10] We have developed a model of the cardiac consequences of stroke in the urethan-anesthetized rat[11] and have demonstrated increased plasma norepinephrine (NE) concentration and sympathetic nerve activity and an incidence of fatal cardiac arrhythmias following middle cerebral artery occlusion (MCAO).[12,13] Using this model, the present experiments compare the sympathetic consequences of right MCAO (RMCAO) and left MCAO (LMCAO) to test for cerebral lateralization of the sympathetic consequences of stroke. A preliminary report of this investigation has been presented in abstract form.[14]

See also p 690.

MATERIALS AND METHODS

General Surgical Procedures

The experiments were carried out on 48 male Wistar rats with weights that ranged from 305 to 455 g. They were divided into two experimental groups (RMCAO and LMCAO) and one group was given sham operation (SHAM).

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The rats were made to fast approximately 16 hours before surgery but were given drinking water ad libitum. They were initially anesthetized with 1.5 g/kg urethan, which was supplemented (0.5 g/kg) during the early surgical part of the experiment only. In these circumstances, an adequate level of anesthesia could be maintained for the duration of the experiment, which continued for 4 hours after general surgical preparation. The right femoral artery and vein were cannulated for measurement of arterial blood pressure and for the administration of drugs, respectively. Pulsatile arterial pressure was measured using a transducer (Statham P23D, Gould Electronics, Florissant, Mo) and monitored on a polygraph (Grass model 7C, Grass Instruments, Quincy, Mass). Mean arterial pressure (MAP) was measured by filtering the pulse pressure with a 0.5-Hz high-frequency filter. Heart rate was determined from the pulse pressure using a tachograph (Grass 7P44, Grass Instruments) and continuously monitored on the polygraph. The trachea was cannulated, and the rat breathed room air.

To occlude the MCA, the head of the rat was placed in a Kopf stereotaxic frame (David Kopf Instruments, Tujunga, Calif). The left or right MCA was approached through an incision made in the skin over the frontalis muscle that extended from the corner of the eye caudally to just anterior to the ear. The frontalis muscle and the temporalis muscle were reflected anteriorly to expose a large portion of the squamosal bone. Removal of a portion of the bone, and exposure and occlusion of the MCA, were done with the aid of a Zeiss operating stereomicroscope (Carl Zeiss, Oberkochen, Germany). A round burr hole (5 mm in diameter) was made in the rostral ventral part of the squamosal bone to expose the MCA. The burr hole was situated approximately 3 to 4 mm dorsal to the foramen ovale and 1 to 2 mm anterior to the point where the zygoma fuses to the squamosal bone. A small portion of the dura over the MCA was cut and retracted using the tip of a 30-gauge hypodermic needle. The MCA was dissected free from the pia-arachnoid and permanently occluded in rats using bipolar coagulation at a point 2 mm ventral to the rhinal fissure and also at a point immediately proximal to the bifurcation of the MCA distributing to the frontal, parietal, and some portions of the occipital cortex.

The remaining rats were sham stroke controls. These rats were prepared as above, except that the MCA was not occluded.

Renal Sympathetic Nerve Recordings

The branches of the right renal nerve were exposed using a retroperitoneal approach. The branch of the renal nerve that joins the prevertebral plexus at the greater splanchnic nerve or ganglion, as described by Sripairojthikoon and Wyss,[15] was isolated from the renal artery, ligated, and cut distally. The nerve was placed on a bipolar stainless steel recording electrode and covered with dental impression material (Perfourm, Miles, South Bend, Ind). Multiunit nerve activity was amplified (Neurolog NL100, Medical Systems, Greenvale, NY) and the discriminated activity displayed on an oscilloscope for observation. The renal nerve activity was rectified, integrated, and continuously monitored on the polygraph. At the end of the experiment (following the last blood sample and immediately before saline perfusion), the ganglionic blocker hexamethonium (2 mg/kg) was administered to determine a value for noise in the nerve recording.

Blood Analyses

Blood samples (0.6 mL) were taken from the femoral artery cannula by a syringe at 10 minutes before MCA occlusion as well as at 1 and 4 hours after MCA or sham occlusion. The blood was transferred to microfuge tubes that had been rinsed with an aqueous preservative solution containing glutathione (60 mg/mL) and EGTA (ethylene glycol-bis, β-aminoethyl ether, *N,N'*-tetraacetic acid) (90 mg/mL). Immediately following collection, the plasma was separated from the cells and frozen at −80°C. Unconjugated NE and epinephrine (E) were measured in duplicate using the radioenzymatic assay CATAKIT (Upjohn, Kalamazoo, Mich), modified as previously described.[11] Assay sensitivities, calculated as the amounts of catecholamine needed to produce a sample disintegrations per minute–blank ratio of 2, were 0.04 pmol for NE and 0.03 pmol for E. In addition, pH, P_{CO_2}, and bicarbonate levels were measured using a blood gas analyzer (Corning 170, Ciba Corning, Corning, NY) on initial blood samples and on final blood samples collected at 4 hours following MCAO or SHAM.

Electrocardiographic (ECG) Monitoring

The ECG monitoring was in the lead II configuration. The PR and QT intervals were measured 15 minutes before and at 1-hour intervals after the MCA or sham MCA occlusion. During the experiment, the ECG monitoring was done continuously on the oscilloscope. The polygraph was run at a high speed (100 mm/s) to obtain records for the measurement of the ECG intervals.

Histological Procedures

The MCA-occluded rats were perfused through the aorta with 0.9% saline, followed immediately by a slow perfusion for about 1 hour with 150 mL of a 2% solution of 2,3,5-triphenyl-2H-tetrazolium chloride (TTC) (Mallinckrodt, Paris, Ky) in normal saline. The TTC reacts with mitochondrial oxidative enzyme systems on mitochondrial cristae and is reduced to form a bright red color in intact cells. Following the TTC solution, the rats were perfused with 4% formaldehyde solution. In these rats, the brains were removed and 1-mm frozen sections were cut on the microtome with 10 sections cut at 50 μm between the 1-mm slices. The 1-mm sections were viewed with light-field optics using a Leitz Diaplan microscope (Wild Leitz, Heerbrugg, Switzerland) and the sections were drawn using a camera lucida attachment. Calculations of the area of the infarct were made from the drawings using a computerized area measurement system (Sigmascan, Conte Madera, Calif). The 50-μm sections were mounted on glass slides and counterstained with 0.125% thionine solution at room temperature and covered with a coverglass with DPX mounting medium (BDH Chemicals, Toronto, Ontario). All thionine-stained sections were examined with a Leitz Diaplan microscope using bright-field optics. The hearts were excised and cut in the axonal plane at 3-mm intervals. These sections were then embedded in paraffin, and sections 5 μm thick were cut on a microtome and stained with hematoxylin-eosin.

Statistical Analysis

Statistical comparisons were made using analysis of variance and either Duncan's multiple range test or a paired *t* test; a *P* value of less than .05 was considered to indicate significance. Values are expressed as mean±SE.

RESULTS

Cardiovascular Variables

The initial MAP values of the SHAM, RMCAO, and LMCAO groups before stroke were not significantly different. The initial values were as follows: SHAM, 90.0±6.4 mm Hg; RMCAO, 72.0±6.1 mm Hg; and LMCAO, 71.2±4.2 mm Hg. However, following SHAM or MCAO, the pattern of change in arterial pressure differed between the groups (Fig 1). The SHAM group rats exhibited a nonsignificant decline in MAP during the experiment. The LMCAO group rats demonstrated a smaller decrease in arterial pressure. This decrease in MAP in the SHAM group with less of a change in the LMCAO group is typical of urethan-anesthetized rats under these conditions.[11] The RMCAO group, however, did not show any decrease in MAP. On the contrary, after 4 hours, a significant increase in MAP was observed compared with the SHAM group rats (Fig 1, bottom).

The heart rates in the three groups before MCAO were as follows: SHAM, 390±8 beats per minute; RMCAO, 378±18 beats per minute; and LMCAO, 376±18 beats per minute. These initial values were not significantly different. No significant change in heart rate occurred after MCA occlusion (data not shown).

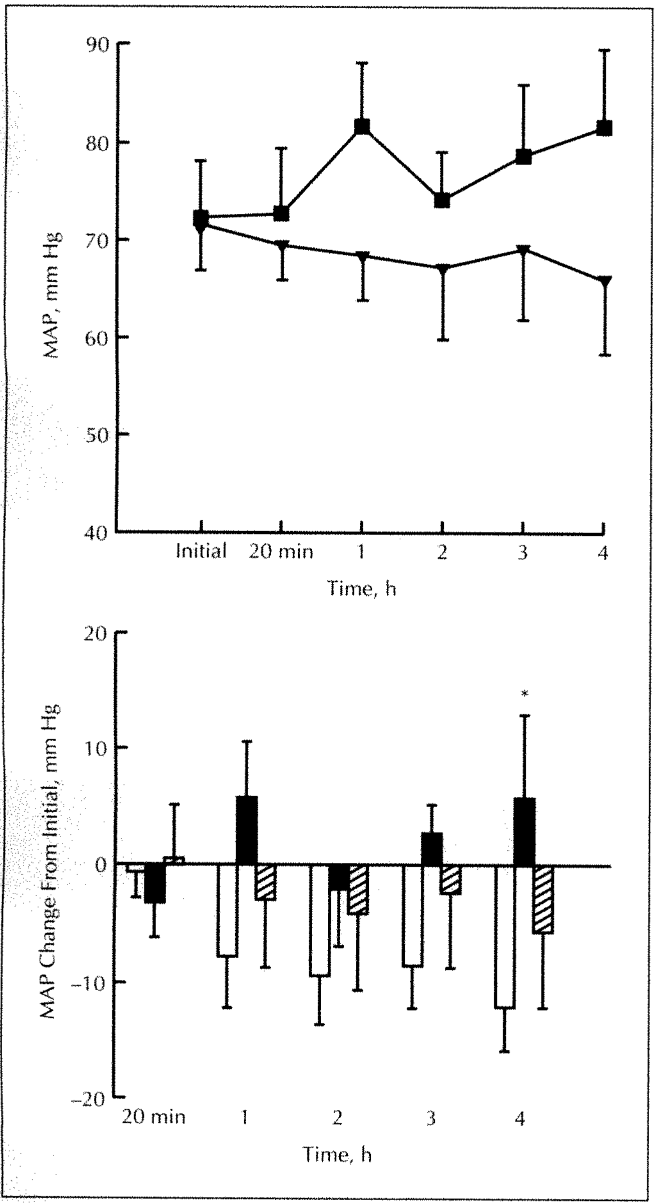

Fig 1.—*Top, Mean arterial pressure (MAP) in Wistar rats with a right middle cerebral artery occlusion (RMCAO) (squares) or a left middle cerebral artery occlusion (LMCAO) (triangles). The values were taken 30 minutes before RMCAO or LMCAO and 20 minutes and 1, 2, 3, and 4 hours after. Bottom, Absolute change in MAP value from initial in Wistar rats with an RMCAO (closed bars), LMCAO (hatched bars), or sham occlusion (SHAM) (open bars). The values were calculated at 20 minutes and 1, 2, 3, and 4 hours after the RMCAO, LMCAO, or SHAM occlusion. Asterisk indicates a significant difference* ($P<.05$) *between the RMCAO and SHAM groups.*

Renal Sympathetic Nerve Activity

Initial levels of integrated sympathetic nerve activity did not differ significantly between groups, and the values were as follows: SHAM, 7.4±2.0 μV/s; RMCAO, 11.3±2.6 μV/s; and LMCAO, 8.8±1.4 μV/s. In the SHAM group, sympathetic nerve activity fell below the initial value within 1 hour and remained depressed for the remainder of the experiment. The LMCAO group exhibited a significant increase in sympathetic nerve activity compared with the SHAM group from 20 minutes to 2 hours following MCA occlusion (Fig 2). The RMCAO group also demonstrated a significant increase in sympathetic nerve activity compared with the SHAM group. This increase was apparent at 20 minutes following the stroke and continued to the end of the experiment (4 hours).

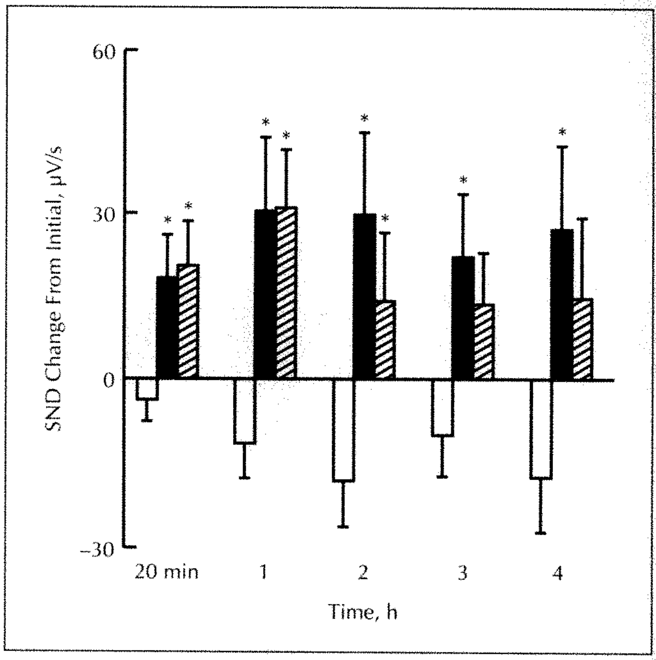

Fig 2.—*Absolute change in integrated sympathetic nerve discharge (SND) from initial in Wistar rats with a right middle cerebral artery occlusion (RMCAO) (closed bars), left middle cerebral artery occlusion (LMCAO) (hatched bars), or sham occlusion (SHAM) (open bars). Values were calculated 20 minutes and 1, 2, 3, and 4 hours after RMCAO, LMCAO, and SHAM occlusion. Asterisk indicates a significant* ($P<.05$) *difference between RMCAO or LMCAO and SHAM.*

Plasma Catecholamines and Blood Gases

Plasma NE levels before stroke were not significantly different between groups and were as follows: SHAM, 11.74±0.90 nmol/L; RMCAO, 10.13±2.03 nmol/L; and LMCAO, 10.67±2.05 nmol/L. No change in plasma NE level was seen in the SHAM or LMCAO groups during the experiment. In contrast, plasma NE levels were significantly elevated by 1 hour (93% above the initial value) in the RMCAO group and remained significantly increased (44% above baseline) at 4 hours (Fig 3).

Initial plasma E levels did not differ between groups, and no change in E value was seen during the 4 hours of the experiment (Fig 4). There were also no changes observed in the P_{O_2} and P_{CO_2} levels during the experiment. The initial values for P_{O_2} were as follows: SHAM, 92±7 mm Hg; RMCAO, 95±4 mm Hg; and LMCAO, 101±5, mm Hg. The initial values for P_{CO_2} were as follows: SHAM, 42±3 mm Hg; RMCAO, 47±4 mm Hg; and LMCAO, 43±3 mm Hg.

ECG Changes

There were no changes in the PR interval in any of the groups during the experiment, and the values did not differ between groups. Initial QT intervals (SHAM, 91±1 milliseconds; RMCAO, 89±3 milliseconds; and LMCAO, 93±3 milliseconds) were not significantly different. A significant lengthening of the QT interval was noted only for the RMCAO group at 4 hours after stroke and attained a 17% increase over the initial value (Fig 5).

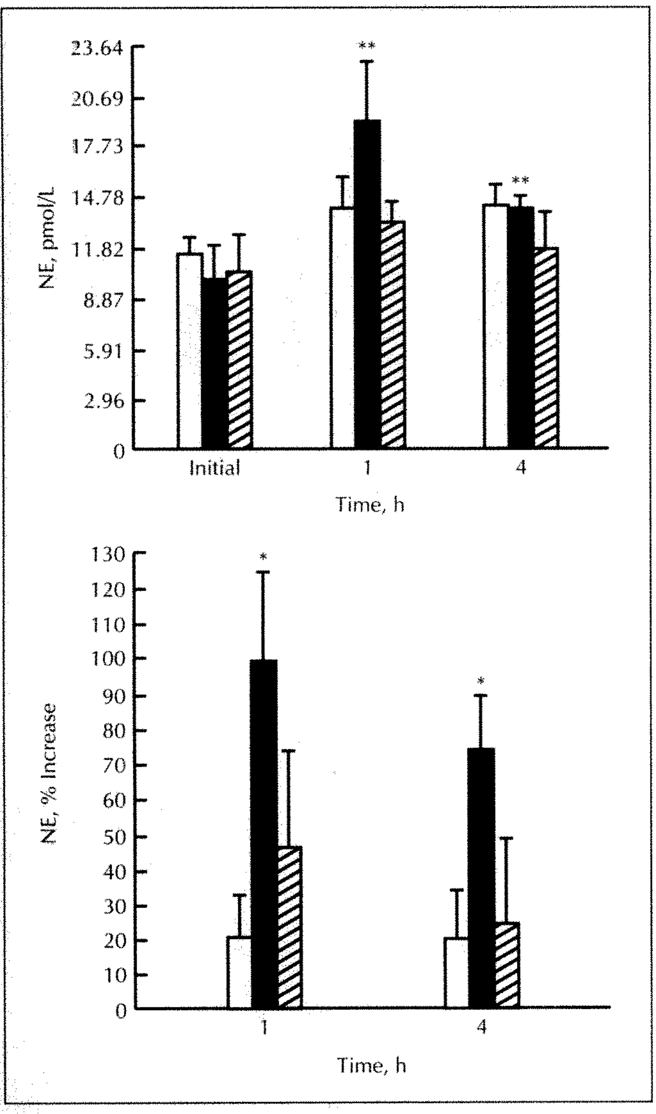

Fig 3.—*Top, Effects of right middle cerebral artery occlusion (RMCAO) (closed bars), left middle cerebral artery occlusion (LMCAO) (hatched bars), and sham occlusion (SHAM) (open bars) on plasma norepinephrine (NE) concentrations measured with a radioenzymatic assay in Wistar rats. Arterial blood samples were taken 30 minutes before and 1 and 4 hours after RMCAO, LMCAO, and SHAM occlusion. Double asterisks indicate a significant change ($P<.05$) within a group from initial. Bottom, Percent increase in plasma NE levels from initial in rats with RMCAO, LMCAO, or SHAM occlusion. The values were calculated at 1 and 4 hours after the RMCAO, LMCAO, or SHAM occlusion. Asterisk indicates a significant difference ($P<.05$) between RMCAO and SHAM.*

Histological Changes

The volumes of the MCAO-induced lesions did not differ significantly between the two hemispheres, and the right and left MCAOs resulted in symmetrical infarcts. The areas involved in the cerebral infarct were similar to those previously reported[11] and include the insular, portions of the perirhinal, frontolateral, motor, primary and secondary sensory, and auditory cortex.

Early histological changes were seen in the hearts of three of the RMCAO, two of the LMCAO, and three of the SHAM group rats. These changes included subepicardial congestion, subendocardial hemorrhage, and the presence of wavy and irregular fibers.

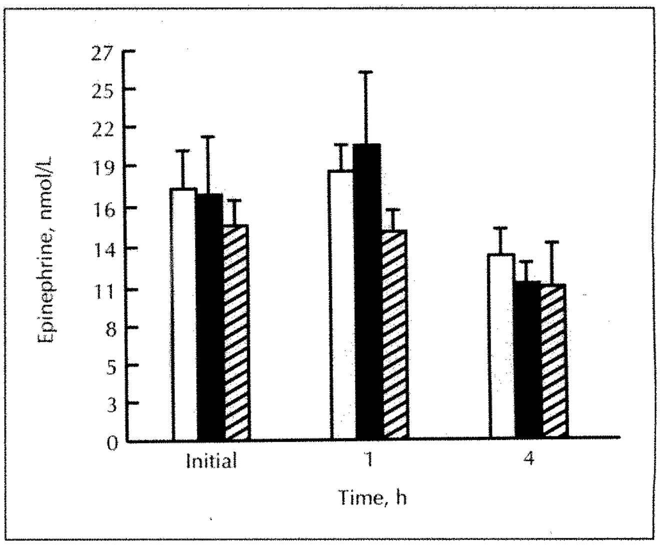

Fig 4.—*Effects of right middle cerebral artery occlusion (RMCAO) (closed bars), left middle cerebral artery occlusion (LMCAO) (hatched bars), or sham occlusion (SHAM) (open bars) on plasma epinephrine concentration measured with a radioenzymatic assay. Arterial blood samples were taken 30 minutes before and 1 and 4 hours after RMCAO, LMCAO, or SHAM occlusion.*

COMMENT

The variables that we have measured are greatly influenced by sympathetic activity. However, it is recognized that some, such as the MAP, heart rate, and QT interval, reflect a complex interplay of sympathetic and parasympathetic activity as well as other factors.

Moreover, urethan tends to decrease blood pressure and increase plasma catecholamine levels,[16,17] giving a high baseline for sympathetic activity. This narrows the range within which changes in sympathetic activity induced by other interventions can be observed. Nevertheless, the model provides a direct comparison of sympathetic and cardiovascular consequences of infarction in the right and left cerebral hemispheres. The tendency for the MAP to drop under urethan anesthesia and for MCA occlusion to delay and moderate this drop, as seen in the comparison of the SHAM and LMCAO groups, we have observed before.[11]

The RMCAO group showed an actual rise in MAP at 4 hours, which coincides with a significant rise in the plasma NE levels, suggesting that the increase in MAP is due to the raised plasma NE levels and hence due to increased sympathetic activity.

Sympathetic nerve discharge (SND) from the right renal nerve rose in the experimental groups. The SND values in the experimental groups were maximal at 1 hour and tended to decrease with time. However, the SND values in the RMCAO group remained significantly higher than in the SHAM group at 3 and 4 hours after stroke, while the value in the LMCAO group did not. It remains unclear whether this is a right or a left hemisphere effect. The majority of the sympathetic hypothalamic projections to the spinal cord are ipsilateral.[18] Since we did not measure the left renal SND, we cannot be sure that the increased SND in the right renal nerve is a right hemisphere lesion effect, but such an interpretation would be in keeping with other measures of increased sympathetic tone in RMCAO group rats, such as the increased plasma NE and MAP values. Technical limitations in our experiments prevent the measurement of cardiac sympathetic nerve activity. However, the change in renal nerve activity is considered reflective of changes in general sympathetic tone. Proportionate responses of arterial NE correlate with proportionate changes in SND in anesthetized adrenal-demedullated rats.[19]

Initial values of arterial plasma NE and E were similar to those we observed in an earlier study of urethan-anesthetized young adult rats.[12] The present study confirmed, in a separate series of rats, that LMCAO of young adult rats does not affect arterial NE within 4 hours. A striking finding is that RMCAO elicits a large and significant increase in arterial NE. An asymmetric representation in the brain of sympathetic function appears to be the most likely explanation for these differing catecholaminergic responses to left and right hemispheric occlusion. The greater rise in plasma NE in the RMCAO group suggests a differential effect on sympathetic activity of RMCAO rats since the location and size of the infarcts was comparable in the RMCAO and LMCAO groups.

The source of the NE is likely to be neurogenic. Considerable NE may be secreted from the adrenal medulla under some circumstances.[20] However, it would be expected that enhanced adrenal secretion would elevate circulating levels of both NE and E. In the present experiments, only the plasma concentration of the neurotransmitter NE was increased following RMCAO, whereas the plasma concentration of the hormone E was not affected by stroke.

Elevation of plasma NE is one of the most reliable predictors of mortality due to heart failure.[21] These pathological catecholamine levels may directly injure the myocardium and cause arrhythmias.[22]

The increase in the QT interval in the RMCAO group rats may be the first manifestation of changes leading to fatal cardiac arrhythmias. In a previous set of experiments, eight of 12 mature adult (186 to 245 days old) rats with MCA occlusion died before the experiment's completion. This group was the only one, compared with two younger groups of rats given MCA occlusion and sham operation, to show a significant increase in the QT interval. The mature adult rats that died showed the highest level of sympathetic nerve activity, suggesting that the QT prolongation and the fatal arrhythmias are mediated through increased sympathetic activity.[12] We have produced prolonged QT interval and fatal arrhythmias by stimulation of selected sites of the rat's insular cortex, probably due to increased NE release in the myocardium and damage to the heart's conducting system.[23]

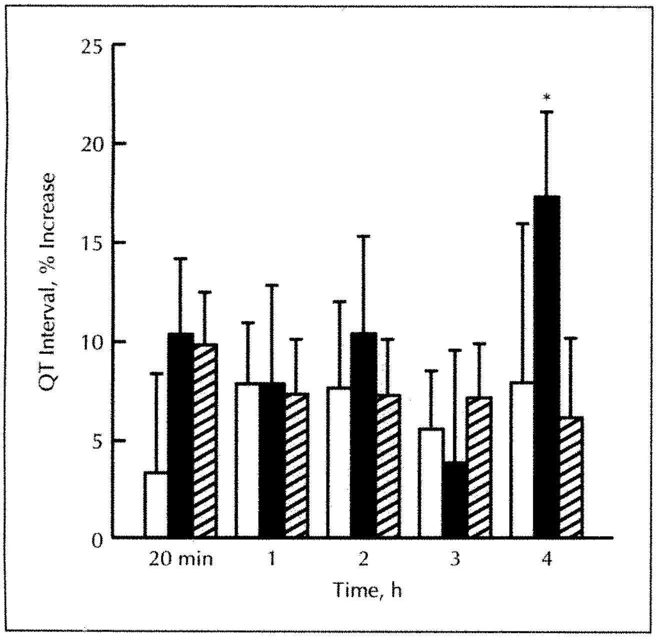

Fig 5.—*Percent increase in QT interval from initial was calculated in Wistar rats with right middle cerebral artery occlusion (RMCAO) (closed bars), left middle cerebral artery occlusion (LMCAO) (hatched bars), and sham occlusion (open bars). Values were calculated at 20 minutes and 1, 2, 3, and 4 hours after occlusion. Asterisk indicates a significant difference (P<.05) between RMCAO and LMCAO.*

The importance of the insula in the mediation of the sympathetic consequences of experimental stroke was first suggested by our experiments in cats, in which cats with cerebral infarcts that spared the insula were not different from cats given sham operation, whereas cats with infarction of the insula showed raised plasma NE level and myocardial damage,[24,25] similar to what has been observed in patients with stroke.[8-10]

Histological cardiac damage was observed in two RMCAO group rats and one each in the LMCAO and SHAM groups. No conclusions can be drawn, but it is possible that differences would emerge if the experiments were longer, since myocytolysis usually requires 6 to 8 hours to develop.[26]

Our results show greater sympathetic consequences (increased plasma NE level and coincident raised MAP level, increased SND value, and prolonged QT interval) with right than with left hemispheric lesions. Our previous work[14,23-25] suggests that it is damage to the insula that mediates the increased sympathetic activity. An asymmetry of sympathetic function would correspond to recognized differential effects on behavior of right vs left hemispheric lesions.[27] Right-sided brain damage has a different effect on emotions than left hemisphere damage. Since emotions involve the sympathetic system, asymmetry of sympathetic effect with right hemispheric damage is not surprising. Robinson[28] described a greater frequency of depression with left hemispheric stroke and postulated that this was explained by the asymmetry of catecholamine content in the brain; that study demonstrated such asymmetry in the rat. Rats with left hemisphere lesions kill mice more frequently than rats with right hemisphere lesions, presumably because a left-sided lesion disinhibits the right hemisphere, which is more activated to kill, arguably from greater fear.[27] Motor sensory asymmetries in experimental infarction in the rat have also been demonstrated recently,[29] adding to the evidence that even in the lissencephalic rat there is differentiation of function between the cerebral hemispheres.

Six percent of patients with stroke die suddenly and unexpectedly from presumed cardiac causes.[30] Since the likelihood of sudden death is not related to the cardiac status or the severity of the stroke and the risk continues for at least 30 days, it becomes difficult to monitor these patients. We have previously shown that damage to the insula appears to be crucial in mediating the sympathetic consequences of stroke.[24,25] The results of the current study show that right hemisphere infarcts have greater sympathetic effects than left hemisphere infarcts. About 32% of patients admitted with stroke show QT prolongation.[31] Previous work and our own studies suggest that QT prolongation may be the prelude to fatal cardiac arrhythmia.[12,23] Hence, on the basis of our experimental data, we postulate that patients with right-sided cerebral infarcts involving the insula and showing QT prolongation would be at the highest risk of sudden death. Clinical confirmation of our hypothesis has practical implications: identification of a small high-risk group makes it practical to institute continuous cardiac monitoring and preventive treatment, a measure that would be economically and logistically forbidding in all patients with stroke.

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Thalamic Stroke

Presentation and Prognosis of Infarcts and Hemorrhages

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- **Thalamic strokes in 62 patients selected from the Stroke Data Bank were studied to determine differences among 18 infarctions (INF), 23 localized hemorrhages (ICH), and 21 hematomas with ventricular extension (IVH). Stupor or coma at onset occurred more frequently in the IVH (62%) than in the INF (6%) or ICH (13%) groups and was reflected in significantly lower median Glasgow Coma Scores in the IVH group (7) than in the INF (15) and ICH (14) groups. Although ocular movements were more frequently abnormal in the IVH group compared with the ICH and INF groups, no significant differences were found in the frequency of motor or sensory deficits. Among the 62 strokes, 32 had restricted lesions of the posterolateral (n=9), anterior (n=3), paramedian (n=7), and dorsal (n=13) portions of the thalamus. Differences in consciousness and in motor, sensory, and oculomotor deficits were found among the topographic subgroups. Stroke-related deaths occurred in 52% of IVH cases, 13% of ICH cases, and no cases of INF. Median lesion volume as detected with computed tomography was greater in hemorrhages (INF, 2 cm^3; ICH, 10 cm^3; IVH, 16 cm^3), with mortality related to increasing hematoma size. Coma, Glasgow Coma Score lower than 9, weakness score greater than 15 of a possible 30, abnormal ocular movements, and fixed pupils were also associated with stroke-related mortality. We conclude that the initial neurologic syndrome does not discriminate infarcts from intrathalamic hemorrhages. Ventricular extension, however, causes significantly more severe deficits and higher mortality.**

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In 1936, Lhermitte[1] suggested some modifications of the thalamic syndrome originally described by Dejerine and Roussy,[2] stressing differences between ischemic and hemorrhagic lesions, with the motor deficit resolving less rapidly and the hemidysesthesia more constant in thalamic infarcts. Fisher[3,4] emphasized ocular movement abnormalities and moderate aphasia with left hemispheric lesions as additional important features of thalamic hemorrhage. More recent large computed tomographic (CT) series confirmed the clinical findings from prior autopsy studies and demonstrated the significance of hematoma extension[5-7] and location[8,9] for the neurologic syndrome and prognosis. However, the reported mortality of thalamic hemorrhage and the prognostic significance of ventricular bleeding has varied considerably. Because no comparison with the clinical presentation of thalamic infarcts was attempted, the neurologic features of thalamic stroke that distinguish between hemorrhagic and ischemic lesions remained unclear.

The designation of clinical syndromes due to restricted thalamic lesions by either pathologic studies or advanced neuroimaging techniques provided additional information about clinical-topographic associations; however, variations of the presenting symptoms were frequently found. In addition, studies and case reports focusing on distinct deficits, such as hemiataxia,[10-13] aphasia,[14-22] hemineglect,[23-26] or amnesia,[27-30] demonstrated varying intrathalamic lesion locations.

To characterize neurologic and radiologic differences between thalamic infarcts and hemorrhages, we analyzed the clinical presentation, prognostic factors, lesion CT topography, and volume of lesions in 62 patients with thalamic stroke selected from the prospectively collected Stroke Data Bank (SDB) cohort.

MATERIALS AND METHODS

The SDB was an observational study that collected acute-care and follow-up clinical and laboratory data on patients with stroke. The study was designed to provide information about the clinical-neurologic features, course, and outcome of patients hospitalized with acute stroke. The collaborative study involved the Biometry and Field Studies Branch of the National Institute of Neurological Disorders and Stroke, Bethesda, Md, as the coordinating center and four academic hospital centers: University Hospital of Boston (Mass) University Medical Center; Michael Reese Hospital and Medical Center, Chicago, Ill; University of Maryland, Baltimore; and the Neurological Institute of Columbia University, New York, NY.

Each patient in this study was examined by one of the SDB investigators within a week of onset of stroke (initial neurologic ex-

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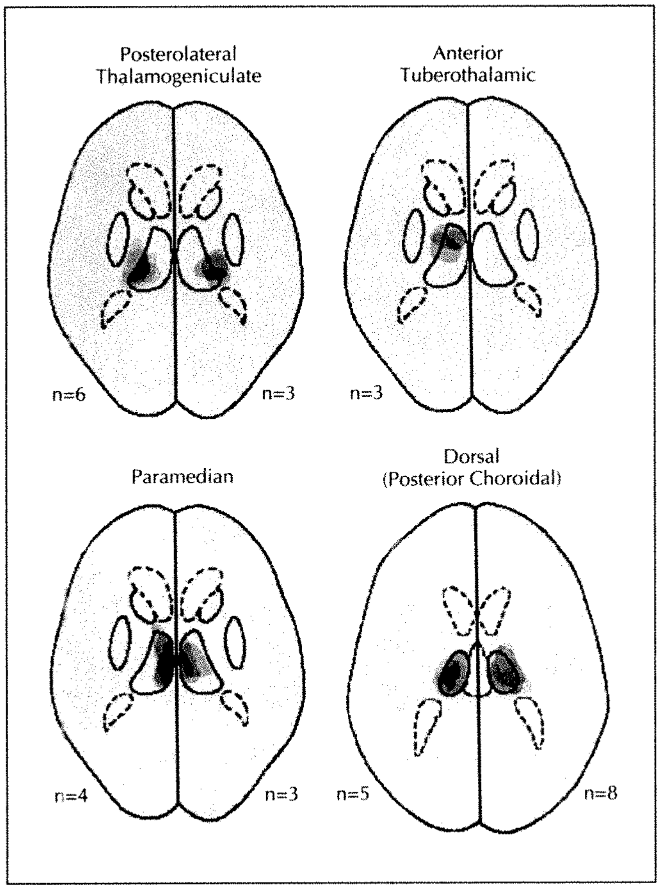

Computer-assisted overlay diagrams of 32 restricted thalamic infarcts and hemorrhages on axial sections 4 (top left, top right, and bottom left) and 5 (bottom right) of the Stroke Data Bank computed tomographic templates and the approximate arterial territories. Shading indicates a greater number of lesions involving the territory.

amination was performed a median of 40 hours after onset) and underwent CT scanning (first CT study was performed a median of 15 hours after onset). For each patient, information concerning medical, neurologic, and social history was obtained; a final diagnosis was made, with special procedures for complications, stroke evolution, stroke recurrence, and death. A full description of the SDB can be found elsewhere.[31]

Patient Selection and Classification

Among the 1805 patients enrolled in the SDB, 94 patients had one symptomatic stroke involving the thalamus that was visualized on the initial CT scan. Patients were selected for the present study if the infarct or the epicenter of the hemorrhage was clearly located within the thalamus and did not extend into the thalamus from another site of origin (n=62). Three subgroups were identified for comparison: 18 infarcts (INF), 23 intrathalamic hemorrhages (ICH), and 21 hemorrhages with ventricular extension (IVH).

For the clinical-topographic analysis, we defined four thalamic areas using planes 4 and 5 of the SDB CT grid and corresponding sections of the thalamus from the stereotaxic atlas by Schaltenbrand and Wahren[32] corresponding to levels 4 mm and 12.5 mm to the intercommissural axial plane and the four different thalamic arterial territories previously described by Percheron[33] and Castaigne et al.[34] Lesions were classified according to the following topographic subgroups (Figure): (1) posterolateral lesions (n=9) approximately in the territory of the thalamogeniculate artery and involving the ventral intermedial, ventroposterior lateral, and ventroposterior medial nuclei; (2) anterior lesions (n=3) approximately in the territory of the tuberothalamic artery and involving the ventroanterior and ventrolateral nuclei; (3) paramedian lesions (n=7) approximately in the territory of the paramedian or thalamoperforate arteries and involving the internal ventro-oral, medial intralamellar, medial, and centromedian nuclei; (4) dorsal lesions (n=13) approximately in the territory of the posterior choroidal artery and involving the anterior, dorsal intermedial, dorsal oral, and upper portions of the medial, pulvinar, and reticular nuclei; and (5) extended lesions (n=30) involving two or more areas. Restricted lesions occurred in 17 infarcts and 15 hemorrhages (median lesion volume, 4 cm^3). Extended lesions were found in one infarct and 29 hemorrhages (median lesion volume, 16 cm^3). Classification and selection of small lesions were performed independently by two investigators (W.S. and R.L.S.), resulting in a 95% agreement (n=59). Three lesions were reclassified after discussion.

Table 1.—Demographic Features and Risk Factors for Thalamic Infarcts and Hemorrhages*

	INF (n=18)	ICH (n=23)	IVH (n=21)	P
Demographic features				
Male, %	33	61	62	. . .
Nonwhite, %	67	83	81	. . .
Median age, y	68.5	65	59	. . .
Risk factors, %				
Hypertension	72	83	91	. . .
Diabetes	44	18	5	.01
Myocardial infarction	6	5	11	. . .
Previous TIA/stroke†	38	21	11	. . .

*INF indicates infarcts; ICH, hemorrhages; IVH, hemorrhages with ventricular blood; and TIA, transient ischemic attack.

†Variable was missing or untestable in more than 10% of patients.

Data Evaluation and Statistical Methods

Demographic variables; risk factors, including medical history of hypertension or diabetes mellitus; signs at onset; neurologic findings at admission; and parenchymatous CT lesion volume were compared for group differences, and, if significant, pairwise differences were tested in the three subgroups (INF vs ICH, INF vs IVH, and ICH vs IVH). Sensory findings were analyzed only in patients who were not stuporous or comatose (n=45). Stroke-related mortality was assessed 30 and 90 days after onset (one patient, who made an almost complete recovery, was unavailable for follow-up after discharge from the hospital on day 10).

Nonparametric median tests for median values of continuous variables, χ^2 test of association, and Fisher's Exact Test (two-tailed) for proportions of categorial variables were used to judge statistical significance. In addition, neurologic features of thalamic hemorrhages and blood pressure (BP) on admission were dichotomized and compared to identify associated stroke-related mortality and tested with use of the Cochran-Mantel-Haenzsel statistics. The initial neurologic findings among the five topographic subgroups (posterolateral, anterior, paramedian, dorsal, and extended) were compared descriptively to identify clinical syndromes associated with distinct lesion locations. Because of the small numbers, statistical analysis was not performed to compare these five subgoups.

RESULTS

Demographic Features and Risk Factors

Among the 62 thalamic strokes, 18 were INFs, 23 were ICHs, and 21 were IVHs. Patients with INF had the highest and those with IVH had the lowest median age (Table 1). Hemorrhages occurred more frequently than infarcts in men, and the majority of patients were nonwhite. History of hypertension was common in all three groups, while diabetes was more common in patients with infarcts than in those with hemorrhages. One patient who had IVH was receiving anticoagulant drugs. Although 38% of patients with infarcts and 33% of patients with hemorrhages had a prior transient ischemic attack or stroke, only one patient had an old infarct seen on the CT scan in addition to the thalamic lesion (small contralateral right-sided parietal cortex).

Neurologic Features

A focal deficit was present at onset in all patients in the INF and ICH groups but in only 71% of patients in the IVH group (Table 2). Deficits were noticed on awakening in more than half of the patients in the INF group but in no patients in the ICH group and only 11% of patients in the IVH group. Vomiting and nuchal rigidity were significantly more common in patients in the IVH group compared with those in the ICH group. Seizures were uncommon in both hemorrhagic groups and did not occur in patients with infarcts. The initial systolic and diastolic BPs were higher in both hemorrhagic subgroups compared with the infarct group, but the difference was significant for the median diastolic BP only. The median pulse pressure was not different among the three subgroups.

State of Consciousness

At onset, stupor or coma was significantly more common in patients in the IVH group than in patients in either the ICH or INF groups (Table 3). The median Glasgow Coma Score (GCS) was reduced in the IVH group compared with the ICH and INF groups. Stupor or coma was present in 37% of patients with extended lesions, 43% of patients with small paramedian lesions, and 21% of patients with restricted dorsal lesions. In contrast, the degree of alertness was not severely affected in any patients with anterior or posterolateral infarcts or hemorrhages. The median GCS was 10 in the group with extended lesions. In the four groups with restricted lesions, the median GCS ranged from 12 to 15.

Table 2.—Clinical Features at Onset in Thalamic Infarcts and Hemorrhages*

	INF (n=18)	ICH (n=23)	IVH (n=21)	*P*
Signs at onset, %				
Focal deficit	100	100	71	<.001
Deficit on awakening†	56	0	11	<.001
Severe headache†	12	22	38	. . .
Vomiting†	0	15	35	.01
Seizures	0	10	5	. . .
Nuchal rigidity†	6	14	40	.05
Median blood pressure, mm Hg				
Systolic	160	190	190	. . .
Diastolic	90	110	110	.01; .03‡
Median pulse pressure, mm Hg	70	70	70	. . .

*INF indicates infarcts; ICH, hemorrhages; and IVH, hemorrhages with ventricular blood.

†Variable was missing or untestable in more than 10% of patients.

‡INF vs ICH; INF vs IVH.

Motor Deficits

Motor deficits were associated with most infarcts and hemorrhages; however, the severity of the paresis, expressed in the SDB weakness score, was significantly greater in the IVH than in either the INF or ICH group (Table 4). Weakness was found in all patients with extended, anterior, and posterior lesions, while 40% of paramedian and 17% of dorsal lesions caused no paresis. The median weakness score was highest in the group with extended lesions and ranged from 12 (posterior lesions) to 19 (anterior lesions) in the restricted lesions. No significant difference was detected in the frequency of ataxia between patients with infarcts and hemorrhages, but the number of tested patients was small. Among the topographic subgroups, the highest frequency of ataxic symptoms was seen in patients with posterior lesions.

Sensory Deficits

Sensory abnormalities were common in patients with both infarcts and hemorrhages, but the median SDB sensory score was higher in the ICH and IVH groups compared with the INF group (Table 5). In two of three patients with anterior lesions, in all patients with posterior lesions, and in 95% of patients with extended lesions, a sensory deficit was present, while in 50% of patients with paramedian and 40% of patients with dorsal lesions, the sensory examination yielded normal findings. The median sensory score was highest in patients with posterior and extended lesions. Pure sensory strokes were found in only two patients with small dorsal infarcts. Among the patients with sensory abnormalities, 78% with posterior and 88% with extended lesions, but only 50% with anterior, paramedian, or dorsal lesions, had a complete sensory deficit involving the face, limbs, and trunk. The sensory profile in the nine patients with a restricted deficit was variable and did not provide discrimination among the topographic subgroups.

Ocular Movement Abnormalities

Abnormal eye movements were more frequently found in patients with IVH than in those with INF or ICH (Table 6). A high percentage of ocular motility abnormalities were diagnosed in patients with extended and paramedian lesions compared with dorsal, anterior, and posterolateral lesions. Horizontal gaze palsy, predominantly gaze preference, was the most common finding in patients with both infarcts and hemorrhages, including two patients with IVH with "wrong-way eyes." Vertical gaze palsy was diagnosed in 11% of patients with INF, 17% of patients with

Table 3.—State of Consciousness on Admission in Thalamic Infarcts and Hemorrhages*

	INF (n=18)	ICH (n=23)	IVH (n=21)	*P*	Post (n=9)	Ant (n=3)	Med (n=7)	Dor (n=13)	Ext (n=30)
Stuporous, comatose, %	6	13	62	<.001	0	0	43	23	37
Median GCS	15	14	7	0.02†	12	15	15	14	10

*INF indicates infarcts; ICH, intrathalamic hemorrhage; IVH, hemorrhage with ventricular extension; Post, posterolateral lesions; Ant, anterior lesions; Med, paramedian lesions; Dor, dorsal lesions; Ext, extended lesions and GCS, Glasgow Coma Score.

†INF vs IVH.

Table 4.—Motor Deficits on Admission in Thalamic Infarcts and Hemorrhages*

	INF (n=18)	ICH (n=23)	IVH (n=21)		*P*
Motor deficit, %	89	95	93		. . .
Median weakness score	12	15	30		<.001; <.001‡
Ataxia, %†	36	18	0		. . .
	Post (n=9)	**Ant (n=3)**	**Med (n=7)**	**Dor (n=13)**	**Ext (n=30)**
Motor deficit, %	100	100	60	83	100
Median weakness score	12	19	15	17	26
Ataxia, %†	38	0	25	29	14

*INF indicates infarcts; ICH, intrathalamic hemorrhage; IVH, hemorrhage with ventricular extension; Post, posterolateral lesions; Ant, anterior lesions; Med, paramedian lesions; Dor, dorsal lesions; and Ext, extended lesions.

†Variable was missing or untestable in more than 10% of patients.

‡INF vs ICH; INF vs IVH.

Table 5.—Sensory Deficits on Admission in Thalamic Infarcts and Hemorrhages*

	INF (n=17)	ICH (n=20)	IVH (n=8)	*P*	Post (n=9)	Ant (n=3)	Med (n=4)	Dor (n=10)	Ext (n=19)
Sensory deficit, %	82	85	75	. . .	100	67	50	60	95
Median sensory score	10	12	14	.02†	12	8	5	5	12

*Stuporous and comatose patients were excluded. INF indicates infarcts; ICH, intrathalamic hemorrhage; IVH, hemorrhage with ventricular extension; Post, posterolateral lesions; Ant, anterior lesions; Med, paramedian lesions; Dor, dorsal lesions; and Ext, extended lesions.

†INF vs ICH.

Table 6.—Ocular Movement Abnormalities on Admission in Thalamic Infarcts and Hemorrhages*

	INF (n=18)	ICH (n=23)	IVH (n=21)	*P*	Post (n=9)	Ant (n=3)	Med (n=7)	Dor (n=13)	Ext (n=30)
Abnormal ocular movement	33	44	77	.03	11	33	86	38	57
Horizontal gaze palsy	28	22	47	. . .	11	33	71	31	27
Vertical gaze palsy	11	17	47	. . .	0	33	29	25	28
Third-nerve palsy	17	9	14	. . .	0	33	17	0	8
Skew deviation	11	9	17	. . .	0	0	40	8	15
Horizontal nystagmus	0	9	13	. . .	0	0	0	0	15
Vertical nystagmus	0	4	0	. . .	0	0	0	0	4
Fixed pupils	0	9	35	.007	11	0	29	23	8

*Values are percents. INF indicates infarcts; ICH, intrathalamic hemorrhage; IVH, hemorrhage with ventricular extension; Post, posterolateral lesions; Ant, anterior lesions; Med, paramedian lesions; Dor, dorsal lesions; and Ext, extended lesions.

ICH, and 47% of patients with IVH. Among the topographic groups, paramedian lesions had the highest frequency of horizontal and vertical gaze disturbances. In addition, 40% of the patients with paramedian lesions demonstrated skew deviation. Less frequent findings in all subgroups were third-nerve palsy and horizontal or vertical nystagmus. Fixed pupils were found in patients with hemorrhages only; however, they were associated with topographically restricted (posterlateral, 11%; paramedian, 29%; and dorsal, 23%) lesions as well as a few extended lesions (8%).

Neurobehavioral and Visual Field Defects

Among the limited number of patients tested, four demonstrated hemineglect contralateral to the thalamic lesions, two of which were right-sided dorsal infarcts and two of which were left-sided extended Among those patients with language deficits, seven of hemorrhages. eight had extended hemorrhages. The only dysphasic patient with a thalamic infarct had an anterior lesion. The most frequent type of language disturbance was transcortical (n=3); only two patients were globally aphasic, and one patient each had a Broca's and Wernicke's type of aphasia. The language disorder in another patient was not classified. Hemianopia was detected in five patients (INF, 6%; ICH, 16%; and IVH, 20%). No quadrantanopia was diagnosed. All visual field defects were due to extended lesions.

Neurologic and CT Findings and Stroke-Related Mortality

Stroke-related deaths occurred in patients with hemorrhages only, with a significantly higher stroke mortality in patients with IVH compared with those with ICH at 30 days (48% vs 9%, *P*=.006) and 90 days (52% vs 13%, *P*=.009). An initial GCS of lower than 9 and the presence of stupor or coma were significantly associated with stroke-related mortality in patients with ICH and IVH

Table 7.—Stroke-Related Mortality in Restricted Hematoma and Hemorrhages With Ventricular Extension Stratified by Neurologic Findings and Blood Pressure on Admission*

Characteristic	ICH (n=23)	IVH (n=21)	CMHS *P*
Glasgow Coma Score			
<9	66 (3)	85 (13)	<.001
≥9	5 (19)	0 (8)	
Initial stupor/coma			
Present	66 (3)	77 (13)	<.001
Absent	5 (20)	13 (8)	
Weakness score			
>15	27 (11)	61 (18)	<.007
≤15	0 (12)	0 (3)	
Ocular movement			
Abnormal	20 (10)	69 (13)	.02
Normal	8 (13)	0 (4)	
Fixed pupils			
Yes	50 (2)	83 (6)	
No	10 (21)	36 (11)	.02
Pulse pressure, mm Hg			
>65	23 (13)	69 (13)	
≤65	0 (10)	25 (8)	.01
Diastolic BP, mm Hg			
>90	19 (16)	67 (15)	
≤90	0 (7)	17 (6)	.02
Systolic BP, mm Hg			
>170	21 (14)	67 (12)	
≤170	0 (9)	33 (9)	.04

*Values are percents (number of patients evaluated). ICH indicates intrathalamic hemorrhage; IVH, hemorrhage with ventricular extension; CMHS, Cochran-Mantel-Haenszel statistic; and BP, blood pressure.

Table 8.—Computed Tomographic (CT) Lesion Volume and Stroke-Related Mortality in Thalamic Infarcts and Hemorrhages

	INF (n=18)	ICH (n=23)	IVH (n=21)	*P*
Median CT lesion volume, cm^3	2	10	16	<.001†, .003‡
CT lesion volume, cm^3 (stroke-related deaths)§				
<5.0	0 (14)	0 (2)	33 (3)	
5.1-10.0	0 (3)	10 (10)	50 (6)	
>10.1	0 (1)	18 (11)	58 (12)	

*INF indicates infarct, ICH, intrathalamic hemorrhage, and IVH, hemorrhage with ventricular extension.

†INF vs ICH.

‡INF vs IVH.

§Values are percents (number of patients evaluated).

(Table 7). A less strong, but still significant, association was found between fatal outcome and an initial SDB weakness score greater than 15 of a possible 30, abnormal ocular movements, fixed pupils, systolic BP greater than 170 mm Hg, diastolic BP greater than 90 mm Hg, and pulse pressure greater than 65 mm Hg.

The median CT lesion volume was smaller in ischemic lesions compared with both hemorrhagic groups (Table 8). Median lesion volume in topographically restricted lesions ranged between 2 and 6 cm^3, but was 16 cm^3 in patients with extended infarcts and hemorrhages.

Most stroke-related deaths were due to extended lesions (n=9) but also occurred in association with five small hematomas (two paramedian and three dorsal); four of these had ventricular extension. When the lesions were classified into three groups according to their volume (<5.0 cm^3, 5.1 to 10.0 cm^3, and >10.0 cm^3), a direct relationship between stroke-related mortality and lesion volume was obvious. In each of the volumetric categories, however, death occurred more frequently in patients with hemorrhages with ventricular extension.

COMMENT

In this series of thalamic infarcts and hematomas, we attempted to determine neurologic symptoms that might allow discrimination among the conditions. In contrast to the widely accepted view that thalamic hemorrhages generally produce a characteristic clinical syndrome, our study demonstrates that restricted intrathalamic hematomas and infarcts can rarely be distinguished by their initial neurologic presentation. The only difference was a lower median sensory score in patients with ischemic lesions. If ventricular bleeding was present, however, the neurologic syndrome altered dramatically: 62% of these patients were stuporous or comatose and had a GCS lower than 9, 86% had a SDB weakness score of greater than 15, 76% demonstrated ocular movement abnormalities, and 35% had fixed pupils. Thus, the decreased level of consciousness, the severity of the motor deficit, and the high frequency of ocular motility disturbances distinguished IVH from INF.

Patients were included in our study when a thalamic lesion was present on the initial CT scan. Because CT scan resolution may be limited and the median time between stroke onset and CT examination was relatively short (15 hours), it is possible that some very small thalamic infarcts may have gone undetected and that the size of the infarcts may have been underestimated. In addition, involvement of the midbrain in the paramedian infarcts was dificult to assess because of CT scanning technique. These technical limitations, however, did not interfere with detection of hemorrhage or with the topographic classification of the infarcts.

Comparison with the findings from other studies is difficult, because only one[7] among the few large CT series of thalamic hemorrhage[5,6,8] evaluated the significance of intraventricular blood for the initial neurologic syndrome. Corresponding to our results, Weisberg[7] found that 10 of 19 patients with large IVH suddenly had become stuporous or comatose and, therefore, called attention to the association of a decline in consciousness and ventricular hemorrhage. In contrast, in a series of small restricted intrathalamic hemorrhages, only three of 37 lesions produced stupor or coma.[9]

In 56% of patients with ischemic thalamic lesions, but in only 5% of patients with hemorrhages, the neurologic deficit was present on awakening, reflecting the previously reported circadian variation in stroke frequency with a peak during early morning hours.[35] Severe headache at onset was not a predominant feature of thalamic hemorrhages in our study. This observation corresponds to the low frequency of initial headache in two other series.[5,6] Vomiting occurred in patients with hematoma only, but in contrast to the study by Walshe et al,[5] this was not a common finding in our patients.

The risk factor profiles showed a high frequency of hypertension in patients with both infarcts and hemorrhages. This confirmed results from previous studies indicating that hypertension was the major risk factor for intracerebral hemorrhage[36,37] as well as for lacunar infarcts due to small-vessel disease.[36] Moreover, admission BP was significantly higher in our patients with thalamic hematoma. Chen et al[38] suggested that this phenomenon may be indicative of an autonomic response to increased intracranial pressure to maintain adequate cerebral perfusion. The high prevalence (44%) of diabetes among our patients with thalamic infarcts confirmed the significance of this risk factor for small, deep infarcts.[36] In a recent series, 43% of 14 patients with lacunar thalamic lesions had diabetes.[39]

Although the initial neurologic syndrome was not clearly different in patients with infarcts and intrathalamic hemorrhage without ventricular extension, prognosis was worse in the latter group. None of the patients with ischemic lesions and only three patients with restricted hematomas died. Our findings corroborate those of Bogousslavsky et al,[39] who recorded only one sudden death due to pulmonary embolism among a series of 40 patients with thalamic infarcts. Clinical deterioration in the three fatal intrathalamic hemorrhages could not be explained by further active bleeding in two cases, as the repeated CT scans in these two cases did not show increased hematoma volume.

Intraventricular blood was a major prognostic factor that significantly increased stroke-related mortality in this subgroup. Mortality rates were similar to those reported by Simonetti et al,[8] who found a 44% mortality rate among 50 patients with IVH. This figure is lower than that reported in other studies.[5,7] In a recent volumetric study, Young et al[40] confirmed the association of ventricular blood with poor outcome in thalamic hemorrhages and quantified the relationship of the volume of intraventricular clot and mortality.

Hematoma size was another consistent indicator of fatal outcome in several studies.[5-8] In one series,[5] all seven patients with thalamic hemorrhages exceeding 3.3 cm in diameter and the 19 patients in Weisberg's[7] study with lesions larger than 3.0 cm died. Although stroke-related mortality in our study increased with larger lesion volume in both hemorrhagic subgroups, mortality in each volumetric category was lower in patients with restricted hematomas. This suggests that ventricular extension of thalamic hemorrhage may have a greater prognostic implication than lesion volume. However, in a recent study from the SDB cohort in which multilogistic regression analysis was used, both size and intraventricular extension were independent predictors for mortality in supratentorial hemorrhages.[41]

Coma or stupor at onset has consistently been associated with fatal outcome in thalamic hemorrhages.[5,6,8] Seven of 11 stuporous or comatose patients in the series by Walshe et al[5] and four of five patients with initial coma in the study by Barraquer-Bordas et al[6] died. Our results confirmed the significant association of a GCS lower than 9 and stupor/coma on admission with mortality, regardless of the presence of intraventricular blood. In addition, for the two combined hemorrhagic subgroups, an SDB weakness score greater than 15, the presence of abnormal ocular movements, and fixed pupils were significantly associated with stroke-related mortality. Our univariate analysis demonstrated systolic BP greater than 170 mm Hg, diastolic BP greater than 90 mm Hg, and pulse pressure greater than 65 mm Hg to be associated with stroke-related mortality. Multivariate techniques, which were not used in our study because of the relatively small number of patients, have shown increased pulse pressure to be an independent predictor of mortality in intracerebral hemorrhages among patients selected from the SDB.[41,42]

In the present series, five of nine restricted posterolateral lesions were infarcts, four of which extended into the posterior limb of the internal capsule. Because the major portion of these infarcts was within the thalamus, we agree with Percheron[33] and Caplan et al[43] that involvement of the internal capsule in posterolateral thalamic infarcts is probably caused by occlusion of penetrating branches from the thalamogeniculate arteries. The clinical presentation of our patients with posterolateral lesions corresponds to the original description by Dejerine and Roussy[2] and reports from other studies.[39,43-45] All patients had a sensory-motor deficit with a higher SDB sensory score compared with the other restricted lesion locations. None of the patients was stuporous or comatose, and only one had ocular abnormalities consisting of a contralateral gaze preference and a unilaterally fixed pupil. Neurobehavioral disturbances were absent in this group. Ataxia was more common in our posterolateral lesion subgroup. Other investigators have reported that lesions in patients with a predominant ataxic syndrome primarily affected the posterolateral area of the thalamus.[10,11,13]

Only two infarcts and one hemorrhage were restricted to the anterior territory; all were left-sided lesions. These patients initially presented with a moderate weakness, and two had additional minimal sensory deficits. Involvement of the adjacent internal capsule may have accounted for these deficits. One patient had an aphasic syndrome that could not be classified into one of the classic categories. Two patients were lethargic on admission. The neurologic findings in our patients corresponded to previous descriptions in the literature. In their study, Graff-Radford et al[45] included five patients with tuberothalamic lesions in their series of 25 thalamic infarcts and delineated a characteristic neurologic syndrome caused by infarcts in this area. Apart from minor sensory-motor deficits, Graff-Radford et al emphasized neuropsychological disturbances consisting of language deficits, disorientation, and memory disturbance associated with dominant lesions and impaired visuoperceptual performance associated with nondominant lesions as characteristic features of tuberothalamic artery infarcts. Bogousslavsky et al[16] described three patients with corresponding lesions and corroborated the typical features of the syndrome. Other case reports had previously demonstrated aphasia in patients with dominant anterior thalamic lesions.[14,17,21]

Aphasia and hemineglect do not appear to be specific for tuberothalamic lesions. In our series, seven of eight patients with aphasia had extended hemorrhagic lesions that involved the posterolateral thalamic area and the pulvinar in five cases but spared the anterior territory in four. In a correlative analysis of aphasic symptoms and topography of the affected thalamic nuclei, Bruyn[20] demonstrated that the pulvinar and the ventral-posterolateral nuclei were most frequently involved. Aphasia has been reported in two patients with autopsy evidence of infarction in the dorsomedial and lateral posterior nuclei in one case[18] and hemorrhage in the area of the dorsolateral nucleus extending into the upper portions of the pulvinar in the other case.[19]

Among our patients, four had contralateral hemineglect, in two cases due to restricted dorsal infarcts involving the upper portion of the median nuclei and in two cases with large left-sided hemorrhages extending across the internal capsule to the medial aspect of the putamen. Other investigators have reported that impaired visuospatial performance and hemineglect were the major neuropsychological disturbances in nondominant tuberothalamic artery territory lesions.[16,45] Different thalamic areas, however, have been suggested to produce a contralateral neglect syndrome. Watson et al[26] proposed that involvement of the medial thalamic nuclei induced hemispatial neglect because of disturbance of the arousal system. Motomura et al[46] found hemineglect in five patients with hemorrhages confined to the posterior part of the right side of the thalamus. In the most restricted lesion among three thalamic hemorraghes reported by Rafal and Posner,[23] deficits in visuospatial attention were caused by involvement of the lateral posterior, centromedian, and ventrolateral nuclei. In one series, a patient with a paramedian infarct in the dominant hemisphere demonstrated dysphasia and hemineglect.[39]

Among the seven restricted lesions in the paramedian areas, three were unilateral infarcts and four were hemorrhages. Patients in this group had a relatively high frequency of severely decreased consciousness (45%), ocular movement disturbances (86%), and pupillary abnormalities (29%), which exceeded the correponding relative frequencies in extended lesions. Although the predominance of initial stupor or coma and abnormal oculomotor findings is in accordance with descriptions of paramedian infarcts and hemorrhages in the literature,[9,34,39,45,47-49] horizontal eye movements were more affected in our patients than was vertical ocular motility.

The neurologic deficits of patients with lesions confined to the dorsal aspect of the thalamus, including the anterior nucleus, the lateral dorsal nuclei, and the upper portions of the medial nucleus and the pulvinar, have rarely been described. Lesions restricted to the dorsal aspect of the thalamus were not included in the two largest series of thalamic infarcts published to date.[39,48] The territory of the posterior choroidal artery was limited to the lower portion of the pulvinar and the geniculate bodies in one study,[39] although these arteries supply most of the dorsal portion of the thalamus.[33,41] In a series of 37 small thalamic hemorrhages, two lesions were restricted to the dorsal portion of the thalamus.[9] The right-sided hematoma produced constructional apraxia and memory disturbance, and the left-sided hematoma caused a minor transient motor deficit and transcortical aphasia. In our series, two patients in the group with dorsal lesions, consisting of seven ischemic and six hemorrhagic lesions, had right-sided thalamic infarcts associated with hemineglect; however, none of the dominant lesions caused aphasic symptoms. Because the initial clinical presentation in this subgroup was less specific, a distinct neurologic syndrome associated with dorsal lesions could not be delineated from our data.

The results from the combined analysis of 62 ischemic and hemorrhagic thalamic strokes demonstrate that the initial clinical syndrome does not clearly separate infarcts from restricted intrathalamic hemorrhages. Thalamic hematomas with ventricular extension, however, are associated with a significant decrease of the initial level of consciousness and more severe neurologic deficits. Among restricted anterior, posterolateral, paramedian, and dorsal infarctions and hemorrhages, the frequency and severity of distinct neurologic features vary. In our series, extended lesions uniformly accounted for more severe neurologic deficits, including all visual field defects, the majority of language disturbances, and both cases with right-sided hemineglect. The most important factor for stroke-related mortality in our series was ventricular extension of the hemorrhage, which occurs more frequently in extended lesions as well as in small paramedian or dorsal hematomas.

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Biological Significance of Iron-Related Magnetic Resonance Imaging Changes in the Brain

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• Iron, an essential element for basic cellular metabolism, regularly accumulates in certain brain areas in normal subjects and in patients with certain diseases. Magnetic resonance imaging can depict iron deposition, offering a singular opportunity to correlate the regional iron content with the functional status of the human brain in vivo. We studied the relationship between age and the iron-related signal loss on T_2-weighted images in basal ganglia, and observed a strongly significant signal decrease in the globus pallidus at the age of brain development (first two decades of life), but we found no such decrease in later years. Moreover, in healthy adults, subject-to-subject variability was relevant in changes due to iron deposition in magnetic resonance imaging. We found increased signal loss to be associated with poor performance on motor and specific cognitive tasks, suggesting that these image changes can provide functional information with respect to the brain in normal subjects.

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Iron is present in all eukaryotic cells, linked to enzymes such as cytochromes and flavoproteins having an important role in cellular respiration by means of oxidative reactions. Iron is essential for brain energy metabolism, for synthesis of several neurotransmitters, and for brain development and maturation.[1-3] The stored form of brain iron is normally coupled with ferritin, representing a large, finely granular pool. Due to unknown circumstances, certain regions accumulate disproportionately large amounts of iron. In this sense, iron concentration in the globus pallidus (approximately 21 mg/100 g) is greater than in the liver, the main iron storage site (13 mg/100 g).[4] Paradoxically, the ability of iron to promote oxidation is also responsible for many of the toxic sequelae associated with iron accumulation. Iron accumulation can participate in the formation of oxygen free radicals and may either initiate or promote lipid peroxidative processes. This phenomenon is thought to be involved in the pathophysiology of some neurodegenerative diseases.[5-7] Excessive iron deposition is a pathological feature of many neurological disorders (Hallervorden-Spatz syndrome, Parkinson's disease, multisystem atrophy variants, Huntington's disease, and tardive dyskinesia).[2,5,8,9]

Magnetic resonance imaging (MRI) has the ability to depict the brain nuclei that accumulate iron as discrete regions, offering us the opportunity to display in vivo the hazardous "thesaurus" of iron in normal and diseased subjects. Stores of ferritin-binding iron, due to heterogeneity and magnetic susceptibility (T_2) effects, produce signal loss on T_2-weighted and gradient echo images obtained by high-field-strength MRI scanners.[8,10] Areas in which signal loss is related to high concentration of iron are preferentially the nuclei involved in motor control, mainly the basal ganglia. This unique opportunity to map iron in the brains of living subjects makes it feasible to study the correlation between iron-related MRI changes and performance in tasks involving these nuclei in normal subjects and also with the severity of symptoms in pathological states.

Few data are available concerning the biological significance and the functional repercussions of iron-related MRI signal loss from basal ganglia in healthy subjects. In a first approach to this issue, some crucial questions emerge: (1) What is the relationship between age and the signal loss associated with iron deposition? (2) Is there any significant variation in MRI iron-related changes among normal subjects? (3) Does an increasingly dark appearance of basal ganglia reflect any deteriorating performance in motor control or in cognitive functions involving these subcortical structures? Herein, we attempt to answer these questions.

SUBJECTS AND METHODS

Study Design and Subject Selection

Our study was designed in two phases. First, we evaluated MRI studies from subjects with ages covering the entire life span to analyze the age-related signal loss in basal ganglia and to determine intersubject variability of these MRI changes. Second, we selected a group of normal adult subjects within a narrow age interval to study the functional significance of MRI basal ganglia signal loss.

Age-Iron Association.—We analyzed MRI clinical studies from 134 subjects (67 men and 67 women). We consecutively re-

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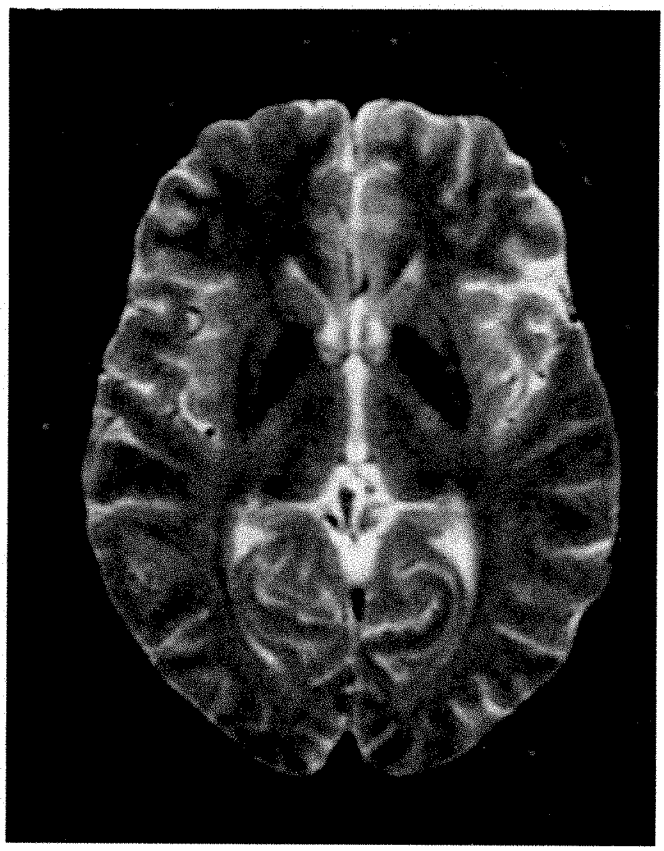

Fig 1.—*Normal appearance of basal ganglia on T_2-weighted images at 1.5 T. Slice selected from routine clinical protocol (repetition time, 2500 milliseconds; echo time, 100 milliseconds) to measure signal intensity in globus pallidus.*

cruited subjects until comparable numbers for each decade of life were obtained. The group encompassed an age range from 8 months to 78 years. We excluded subjects with (1) extrapyramidal disease, (2) diseases with previously reported basal ganglia signal abnormalities, or (3) MRI studies showing basal ganglia lesions.

Iron-Function Relationship.—We selected a second group of 25 optimally healthy subjects who met criteria of no history of neurological disease, normal neurological examination, and absence of cerebrovascular risk factors. In this selection, we stressed that subjects should be at an age for which age-related iron accumulation was mainly established. The mean (±SD) age in this group was 70±3.2 years (range, 65 to 76 years). Sixteen were men and nine were women. The mean level of education attained was 7.8±4.9 years (range, 3 to 18 years).

MRI Procedures

All MRI scans were performed using a superconducting magnet at a field strength of 1.5 T (Signa system, General Electric, Milwaukee, Wis). A field of view of 24 cm, a matrix size of 256×256, and a slice thickness of 5 mm were used in every pulse sequence.

In the age-iron association analysis, images proceeded from the routine clinical image protocol used in our MRI center. We analyzed a single slice containing the globus pallidus from an axial projection (Fig 1). The axial slices consisted of a pure transverse projection (±10° from orbitomeatal line) obtained from a spin-echo pulse sequence with a 2500-millisecond repetition time and 40- and 100-millisecond echo time. This sequence produced heavy T_2-weighted images (second echo) and allowed full expression of the magnetic susceptibility effect at a field strength of 1.5 T.

On our laboratory console, we interactively specified a region of interest that included a representative portion of the globus pallidus, selected randomly from right or left sides (in a pilot study, we found no right-left difference). Signal intensity was measured using a gray scale ranging from 0 to 255. To remove the effect of the system gain settings on signal intensity, we used the method of standardization commonly adopted in densitometer analyses,[11,12] adapted to our requirements: signal intensity from cerebrospinal fluid (CSF) was used as reference pattern, and the system gain was removed using the same procedure as that followed in the partial correlation analysis. Thus, we obtained new values for the globus pallidus signal, applying the following formula: $cGP=GP+(mCSF-CSF)\times Slope_{GP.CSF}$, where cGP is the "corrected" globus pallidus signal, GP the measured globus pallidus signal from a subject, mCSF the mean of CSF signal values from the group of 25 subjects, CSF the measured CSF signal from the same subject, and $slope_{GP.CSF}$ the slope of the regression line of globus pallidus on CSF.

In the second part of the study, we used a distinct MRI protocol that allows accurate transverse relaxation time calculation (image parameter independent of system gain). Here, we evaluated iron-related signal changes on basal ganglia twice, using T_2 relaxation times and corrected-signal intensities. To make the study nonredundant, only the globus pallidus (striatonigral system) and the red nucleus (dentatorubral system) were evaluated. We used a multiecho spin-echo pulse sequence with a 2000-millisecond repetition time and four echoes with an interecho time of 25 milliseconds (25-, 50-, 75-, and 100-millisecond echo time). The images were obtained in the axial plane with defined anatomic references from the sagittal plane. The first slice containing the red nucleus was referred to a line passing through the superior colliculus and the orbital surface of the frontal lobe. The second slice containing the globus pallidus lay parallel and above this reference slice. The interslice gap was 2 mm thick. Again, we selected a region of interest, here from the red nucleus and globus pallidus, and measured signal on each of four images corresponding to different echo times (Fig 2). Corrected signal intensities were computed according to the method described above. In addition, the conventional equation that describes spin echo image intensity[12] was used to obtain an overdetermined equation system (signal intensities from the four images acquired at different echo times), in which T_2 values were estimated with the use of a χ^2 minimization technique.[13]

Neuropsychological Tests

To investigate the functional significance of the iron-related MRI changes, the healthy subjects included in the second study phase received a set of tests to evaluate motor skills and neuropsychological functions involving basal ganglia.

We assessed motor skills using a set of timed tests such as Finger Tapping and Line Tracking included in the Motor Performance Test Series from the Vienna Test System,[14] the Purdue Pegboard Test, Trail Making A, and a simple visual reaction time task.[15] The measurements computed were number of taps for the Finger Tapping Test, length of errors ("closing in" error) in seconds for the Line Tracking Test, number of pins inserted in 30 seconds (right and left hands) for the Purdue Pegboard Test, length of test in seconds for the Trail Making A Test, and time in milliseconds for the simple reaction time.

We administered the Stroop Test and a dual task as tests requiring a high level of attentional control.[16] We used two versions of the Stroop Test[17]: a standard version, in which the verbal response time (milliseconds) was recorded when the subject was required to name the color in which a stimulus word was presented and ignore the meaning of the word (blue, green, red, or yellow); and a modified version, in which, before each stimulus presentation, the subject was asked at random to name either the color in which a stimulus word was presented or the meaning of the word. This version was administered to measure difficulty in making shifts in attention, and in this case the number of errors was computed (shifting errors). In the dual task, subjects were required to tap two keys alternately with the right

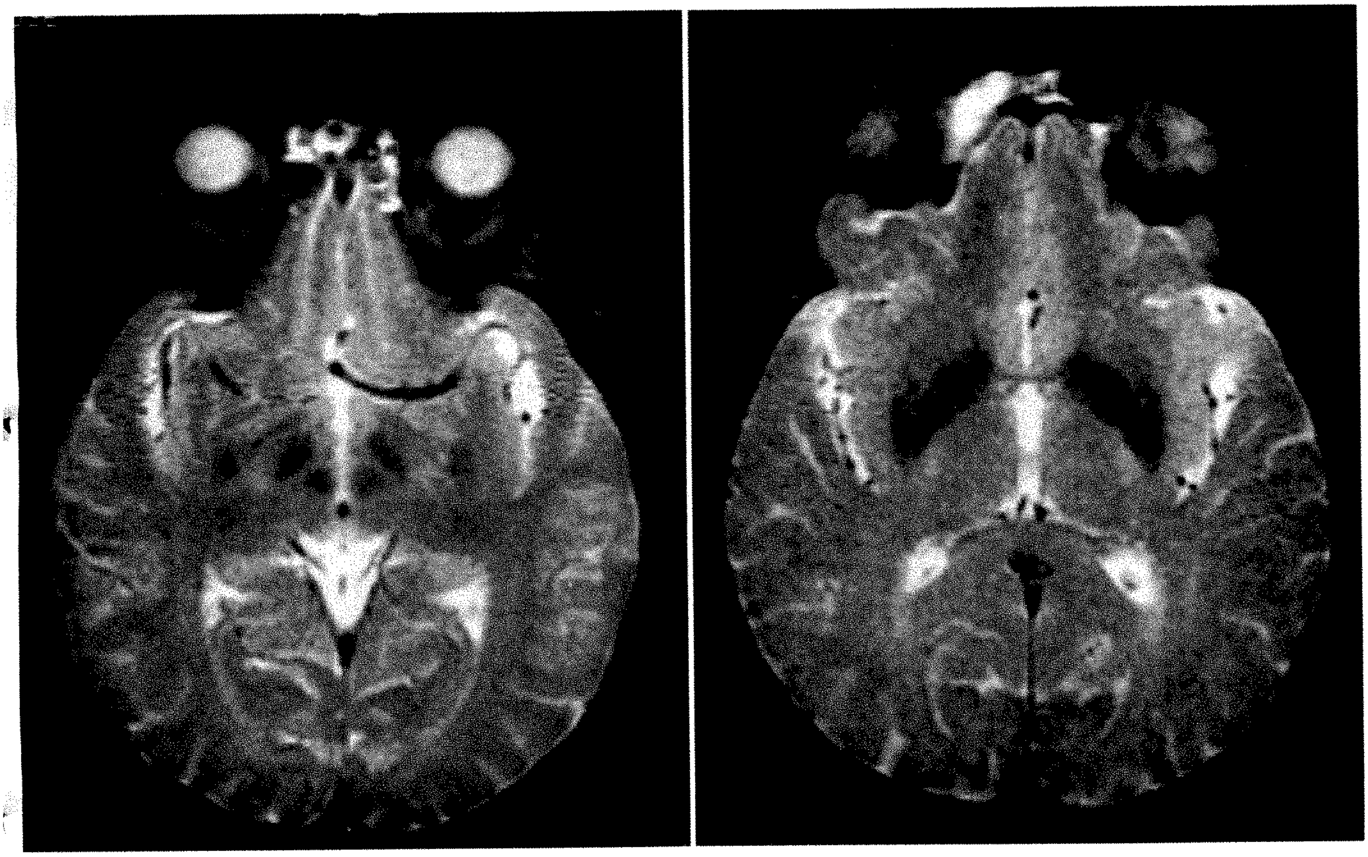

Fig 2.—*The images of fourth echo obtained with a multiecho sequence (repetition time, 2000 milliseconds; echo time, 25, 50, 75, and 100 milliseconds) in which T_2 and signal intensity were measured. Left, Caudal slice showing the red nucleus; right, cranial slice showing the globus pallidus.*

hand while reading a text. The two components of these dual tasks (tapping and reading) were also assessed separately and were used as reference. The difference between the number of taps in the basal and concurrent condition in 20 seconds (decrease of taps when reading) and the number of letters read in the basal and concurrent condition (decrease of letters read when tapping) were recorded. From these data, we computed the interference that reading produced on tapping in the concurrent condition using partial correlation ("tapping controlled for reading").

We tested aspects of learning putatively related with basal ganglia. We assessed procedural learning using a classic mirror-reading task.[18,19] Subjects read five nonrepeated cards with 10 mirror-words in each one. We computed the time taken by the subject to read the last card (this time was corrected by performance on the first card, using partial correlation). We also assessed two aspects of incidental (automatic) learning.[20] First we tested incidental learning of the frequency of occurrence, asking the subject for the number of times that each word appeared in a Brown-Peterson task.[21,22] There were 22 words that appeared from zero to five times. We registered errors of recognition and frequency judgment by summing the differences between the frequency reported by the subject and the real frequency. The full scale of possible errors was from 0 to 75. Second, incidental learning of spatial location was tested, requiring the subject to estimate the location of nine pictures arranged on a 3×3 board that had previously been presented to the subject for memorization, but without instructions to memorize position. The total number of locations correctly identified was recorded as "incidental learning of spatial location."

Statistical Analysis

In the age-iron association analysis, nonlinear regression was used to fit the equations to data. Student's *t* test was applied to test mean differences between sex conditions. The Pearson Product-Moment Correlation Coefficient was used to determine the relationship between performance in each test and MRI measurements.

RESULTS

Age–Signal Loss Relationship in Globus Pallidus

The MRI corrected-signal intensity measured on the globus pallidus from 134 subjects showed a significant negative linear correlation with age ($r=-.69$, $P<.000$) and a stronger correlation with the natural logarithm of age ($r=-.85$, $P<.000$), suggesting an exponential signal decrease (increase in iron deposition). In consequence, we applied a nonlinear curve-fitting algorithm (least squares method) to determine the best parameters to fit an exponential function to data. The following equation was found: Globus Pallidus Corrected Signal=$43.97+54.03\times e^{-0.11\times \text{Age}}$; the norm of residuals was 89.31 (Fig 3). On this analysis, we can see a rapid decrease in signal intensity in the earliest two decades of life, a decrease that was progressively less with advancing age and that finally disappeared (after the age of 40 years). We quantified the rate of signal decrease and found that the signal range (maximum-minimum signal values calculated applying the equation) undergoes a 90% reduction at the calculated age of 20.9 years and a 99% reduction at 41.82 years. We analyzed the data on a separate group including subjects with age greater than 41.82 years (iron accumulation had already reached the highest levels). In this old group ($n=58$), the significance of the correlation between age and corrected-signal intensity of globus pallidus disappeared ($r=-.08$, $P=.254$).

Individual Differences

Differences in iron accumulation among subjects may be represented by the descriptive statistics from this old group (here, variations in signal intensity values were not dependent on age). The mean corrected-signal intensity from the globus pallidus was 43.03±8.23 and ranged from 28.79 to 75.85. As we can observe from these figures (and in Fig 3), there were substantial differences in the globus pallidus MRI appearance in adult subjects. We found no sex differences (mean globus pallidus corrected signal for men was 53.3±14.7 and for women, 49.9±15.4; $t=1.29$, $P=.20$).

Neuropsychological Correlations

We used the calculated T_2 and the corrected-signal intensities from globus pallidus and red nucleus for the analysis of correlations. Due to the image protocol used in this analysis, the variability or ranges of measured values are smaller than the values found on the protocol used in the age-related study. These values are given in Table 1.

Neuropsychological test results are presented in Table 2. Since various correlations were performed (11 separate tests times two brain nuclei), we were rigorously stringent in interpreting isolated correlations at the level of $P<.05$.

We found no definite association between measurements from the iron-containing nuclei and simple motor performance, although, in particular cases, the power of the correlation suggested some relationship. In this respect, image parameters from the globus pallidus correlated with the Finger Tapping at $P<.05$, and signal intensity from the red nucleus correlated with Line Tracking at the same level. We found better results in tasks requiring large attentional demand. The shifting errors on the Stroop Test showed a weak association with measurements from the globus pallidus. Signal intensity from the red nucleus correlated with the dual task tested (tapping while reading) at $P<.01$. On the other hand, we found a strong association between both measurements from the globus pallidus and incidental learning, evaluated using the error in the estimation of frequency on retrieval of previously presented words (Fig 4 illustrates this correlation). In addition, corrected-signal intensity showed a tendency to correlate with performance on incidental learning of spatial location.

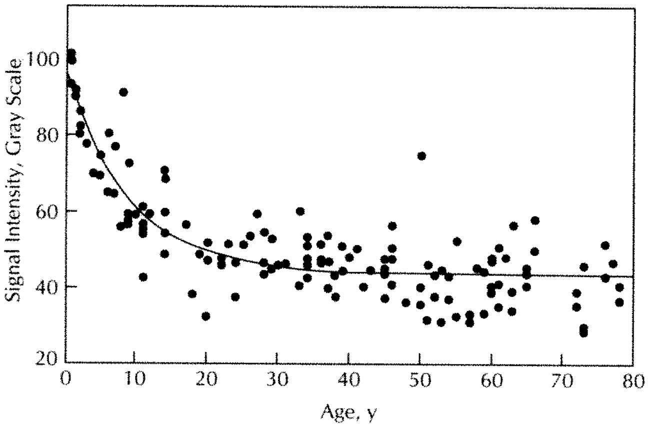

Fig 3.—*The relationship between corrected-signal intensity in the globus pallidus and age. The calculated regression line is represented.*

COMMENT

Iron-containing nuclei are depicted as dark regions on T_2-weighted MRI scans performed at high field strength. Signal loss in the globus pallidus, red nucleus, and substantia nigra (pars reticulata) is evident and invariable and occurs early in life. Image changes in the dentate nucleus of cerebellum are less discrete and inconsistent, and in the striatum a less conspicuous signal reduction appears later.[8,23,24] The signal loss observed varies according to the concentration of macromolecular complexes of iron and the strength of the magnetic field.[24] There appears to be a parallel between the appearance of these brain areas in vivo and qualitative and quantitative measurements of iron in postmortem tissue samples.[4,8,10,24]

Nevertheless, this parallelism is not always found, and it is not found in all parts of the brain. Despite their high iron concentration in adults, the caudate and the ventral medial aspect of the putamen show relatively little loss in signal.[24] On the other hand, the pattern of signal intensity appears modified after death in unfixed brains,[25,26] particularly in nuclei with high iron concentration (according to our own experiments, not reported herein). This is sufficient to produce a lack of correlation between T_2 values from postmortem studies and iron content.[27,28] Taking these findings together with the complex magnetic behavior of iron, it is not only the total amount of iron but also its physical state and environmental interactions that are determining factors on the image appearance of the brain iron-containing nuclei.[26,27] These nuances make interpretation of data somewhat difficult, although they generate a special interest, providing a fine metabolic dimension to the studies on iron-related MRI changes.

To establish the significance of basal ganglia iron accumulation, it is important to determine the relationship between iron concentration and age. Many cumulative pathological changes in the central nervous system become more apparent in late stages of life. Thus, ventricular enlargement, white matter ischemic lesions, and neuropathological senile changes are all examples of events that occur mainly in the elderly. Brain iron deposition is a phenomenon strongly related to age, but it does not occur in old people. Indeed, as reported by Hallgren and Sourander,[4] the low content of brain iron at birth rapidly increases during the first two decades of life, and no further increase oc-

Table 1.—Calculated T_2 Relaxation Times and Corrected-Signal Intensities From Analyzed Anatomic Regions in 25 Normal Subjects

	T_2, ms		Corrected-Signal Intensity	
	Mean±SD	Reference Range	Mean±SD	Reference Range
Globus pallidus	47.2±2.5	42.4-52.0	29.2±2.8	24.2-34.4
Red nucleus	53.4±3.1	45.6-58.1	34.5±3.6	26.9-42.3

Table 2.—Neuropsychological Correlations

		r			
		Globus Pallidus		Red Nucleus	
Test	Mean±SD	T_2	Signal	T_2	Signal
Motor performance					
Tapping	113.0±11.4	.45*	.38*	.19	.17
Line Tracking	5.0±2.0	.05	.07	−.27	−.46*
Purdue Pegboard	25.6±3.95	.12	.14	−.08	.31
Trail Making A	45.2±23.6	.05	.08	.12	−.01
Reaction time	366.9±75.1	−.21	−.14	.00	.12
Attention					
Stroop Test					
Interference	283.8±119	−.23	−.24	.09	.06
Shifting errors	2.4±1.9	−.40*	−.45*	−.31	−.32
Dual task					
Tapping/reading	21.0±13.5	−.14	−.13	−.42*	−.50†
Learning					
Procedural	33.9±27.4	−.05	−.02	−.18	−.01
Incidental					
Frequency	17.0±4.7	−.51†	−.57†	−.18	−.15
Space	8.1±1.8	.10	.34*	−.03	.13

*$P<.05$.
†$P<.01$.

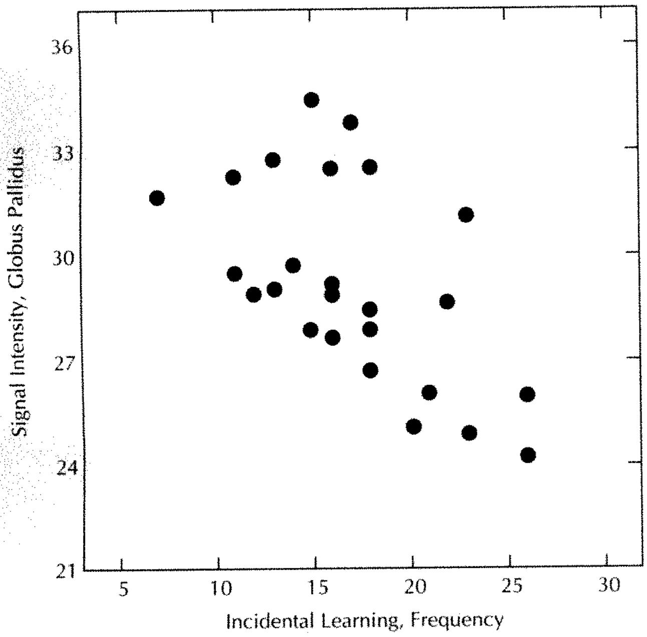

Fig 4.—*Plot representing the relationship between corrected-signal intensity of the globus pallidus and the error in the estimation of frequency.*

curs after the age of 30 years in the globus pallidus, red nucleus, pars reticulata of substantia nigra, or dentate nucleus of the cerebellum. In the putamen and caudate nucleus, the iron content increases somewhat more slowly; these nuclei do not reach maximal levels until the age of 50 to 60 years. Overall, the age–iron content relationship is preferentially a developmental event. Aoki et al[23] determined the normal timing and sequence of MRI signal loss in brain regions that are known to accumulate iron in young subjects. They concluded that qualitative MRI observations in childhood and adolescence were highly comparable with the quantitative biochemical studies of iron. We studied the relation between age and iron in a series of subjects including the entire life span. We used quantitative MRI measurements from a representative iron-containing region, in this case the globus pallidus. Age was strongly associated with signal intensity from this nucleus in the whole series, although this association, strongest in young subjects, disappeared in adults. We found no further decrease of signal after the age of 40 years.

The data illustrated in the plot of age against signal intensity of globus pallidus (Fig 3) are fully in agreement with the results reported by Hallgren and Sourander.[4] This similarity between MRI analysis and data from brains at autopsy indicates that the image measurements may be a useful tool to study the significance of brain iron levels in vivo.

The reciprocal relationship between oxygen consumption of the human brain and brain iron accumulation indicates: the rapid rise in brain iron levels during the first decades corresponds to a rapid decline in oxygen utilization. In the following period, the more gradual fall in oxygen consumption is paralleled by a slower increase in iron levels.[4,29] Due to the implications of iron in the enzyme systems related to energy metabolism, it has been suggested that brain iron accumulation might reflect a general "physiological" decay in oxidative metabolism. In this sense, MRI changes might represent an image indicator of the functional status of brain energy.

Does regional brain iron concentration vary significantly from person to person in normal adults? This is a relevant issue because different rates of iron deposition might be related to both structural and functional status of basal ganglia. We found a great range of signal intensity from globus pallidus in normal adults aged over 41 years. It has yet to be determined whether this normal variability represents an essential feature of the basal ganglia or only an epiphenomenon. On the other hand, although knowledge of the normal range may be helpful in the recognition of iron-related pathological states, the great range of signal intensity in normal subjects makes it difficult to label any case study as pathological based merely on the dark or bright appearance of the globus pallidus, or even the substantia nigra or the red nucleus. In our opinion, the following two patterns are not normal and deserve more accurate clinical evaluation: (1) a very dark appearance of any basal ganglia before the age of 20 years, and (2) a widespread darkening of the striatum at any age showing signal intensity similar to that in the globus pallidus.

We assessed motor skills as functions involving the basal ganglia. We failed to demonstrate any overall correlation between simple motor performance and iron-related MRI measures, although in particular cases the measurements reached a level of significance of $P<.05$. According to these results, we cannot predict poor motor performance in any case showing sensitive signal loss in basal ganglia, but we may interpret darkening of the basal ganglia as a "negative" MRI sign.

A difficult but insightful interpretation emerges from the significant association found between image measurements and some cognitive functions. We found that incidental learning was associated with iron-related changes in globus pallidus. Incidental learning, contrary to intentional, is an automatic or effortless process minimally influenced by intelligence, which operates at maximal level early in life and does not change with age.[20] There is no known anatomical substratum for incidental learning, although the characteristics of this function suggest that subcortical structures play a relevant role in its processing. The other function assessed that reached a noteworthy level of significance was the tapping-while-reading task. This function may share some features with incidental learning because execution of dual tasks needs correct functioning of subcortical structures to their precise and speeded achievement. Patients with a basal ganglia disorder, as in Parkinson's disease, perform worse when an intellectual and a motor task are required together.[16] Furthermore, it is known that symptoms like resting tremor in that disorder can be elicited by asking the patient to perform mental arithmetic.[30]

At present, conclusions beyond a pure description of the findings are speculative. It is not possible to determine whether poor performance in incidental and dual tasks results from neuronal degeneration due to iron accumulation or whether this association is merely coincidental. In the latter case, the MRI-depicted iron status would represent a physiological, perhaps developmental, attribute that covaries with some brain functions. In other words, from our study of correlations, we cannot conclude that the areas involved in excessive iron deposition are necessarily involved in cognitive functioning failure. Furthermore, performance in some nontested functions may exhibit an inverse relation to the iron concentration (more iron, better performance). Supporting this possibility, even if indirectly, is the report from Tucker et al,[31] in which higher levels of serum ferritin were associated with greater verbal fluency but poorer nonverbal auditory task performance.

Finally, we briefly comment some methodological issues. Quantitative studies performed on hepatic tissues demonstrated the utility of MRI as a method for direct noninvasive measurement of human iron stores. Several authors reported a highly significant linear correlation between iron concentration and certain magnetic parameters like magnetic susceptibility measurements ($r=.99$),[32] calculated T_2 relaxation times ($r=.98$),[33] and derived image signal intensity data ($r=.98$).[12] We used two methods to quantify image changes related to regional iron content and found similar results, but results with corrected-signal intensity were slightly superior to those obtained with T_2 determinations. As stated by Stark et al,[12] calculation of T_2 values from signal intensity measurements compounds any error present in these data, and as a result, the precision of T_2 calculations is less than the precision of signal intensity measurements. The main difficulty in using the values from signal intensity arise from the need to remove the system gain. The method used in our study to correct signal intensity using data from CSF as reference is a simple and useful method of standardization easily applicable when analyzing series of image studies.

Knowledge of the precise effect of age on image appearance of iron-containing regions, the statement of normal range of variability among normal subjects, and the recognition of their functional significance, in addition to their biological relevance, are necessary steps for future studies investigating pathological disorders involving abnormal iron accumulation associated with definite MRI changes, such as Hallervorden-Spatz syndrome,[34] Parkinson plus syndromes (multiple-system atrophy variants[35,36]), and multiple sclerosis.[37]

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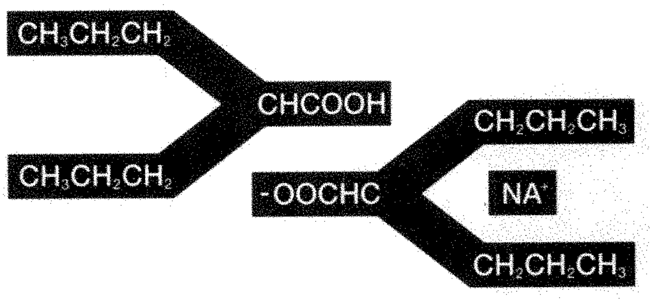

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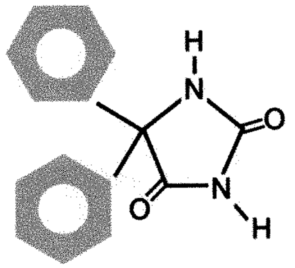

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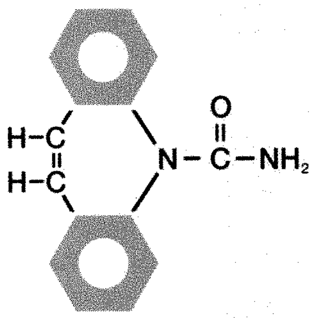

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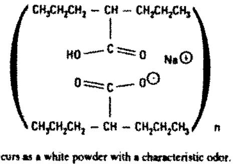

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Inactive Ingredients

125 mg Sprinkle capsules: cellulosic polymers, D&C Red No. 28, FD&C Blue No. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.

DEPAKOTE tablets: cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, and vanillin.

In addition, individual tablets contain:

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CLINICAL PHARMACOLOGY

Divalproex sodium is an antiepileptic agent which dissociates to the valproate ion in the gastrointestinal tract. The mechanism by which valproate exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA).

Equivalent oral doses of DEPAKOTE (divalproex sodium) products and DEPAKENE (valproic acid) capsules deliver equivalent quantities of valproate ion systemically. However, the rate of valproate ion absorption may vary with the conditions of use (eg, fasting or postprandial) and the method of administration (eg, whether the contents of the capsule are sprinkled on food or the capsule is taken intact).

When subjects are in a fasting state, peak plasma concentrations of valproate ion are observed approximately 3 to 4 hours following administration of all DEPAKOTE products.

Experiments indicate that feeding can influence the rate of systemic absorption of valproate. In studies in which the contents of DEPAKOTE (divalproex sodium) Sprinkle capsules were sprinkled on applesauce, feeding was found to delay the time to peak plasma concentration by approximately 1.5 hours.

Compared to DEPAKOTE tablets, however, DEPAKOTE Sprinkle capsules (in the fasting state) exhibit a slower rate of absorption, resulting in lower peak plasma concentrations (ie, fluctuations between minimum and maximum plasma valproate concentrations are attenuated).

While absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate in chronic use is not affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.

Accordingly, coadministration of oral valproate products with food and substitution among the various DEPAKOTE and DEPAKENE formulations should cause no clinical problems (see DOSAGE AND ADMINISTRATION). Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

The plasma half-life of valproate is typically in the range of 6 to 16 hours. Half-lives in the lower part of the range are usually found in patients taking other antiepileptic drugs capable of enzyme induction.

Valproate is primarily metabolized in the liver. The major metabolic routes are glucuronidation, mitochondrial beta oxidation, and microsomal oxidation. The major metabolites formed are the glucuronide conjugate, 2-propyl-3-keto-pentanoic acid, and 2-propyl-hydroxypentanoic acids. Other unsaturated metabolites have been reported. The major route of elimination of these metabolites is in the urine.

Patients on monotherapy will generally have longer half-lives and higher concentrations of valproate at a given dosage than patients receiving polytherapy. This is primarily due to enzyme induction caused by other antiepileptics, which results in enhanced clearance of valproate by glucuronidation and microsomal oxidation. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

The therapeutic range is commonly considered to be 50 to 100 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.[5] Valproate is highly bound (90%) to plasma proteins in the therapeutic range; however, protein binding is concentration-dependent and decreases at high valproate concentrations. The binding is variable among patients and may be affected by fatty acids or by highly bound drugs such as salicylate. Some clinicians favor monitoring free valproate concentrations, which may more accurately reflect CNS penetration of valproate. As yet, a consensus on the therapeutic range of free concentrations has not been established; however, monitoring total and free valproate may be informative when there are changes in clinical status, concomitant medication, or valproate dosage.

INDICATIONS AND USAGE

DEPAKOTE (divalproex sodium) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE WARNINGS FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DIVALPROEX SODIUM SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia, and vomiting. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKOTE products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risks. Above this age group, experience has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage in Pregnancy: ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.[1]

OTHER CONGENITAL ANOMALIES (EG, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TOCONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

ANIMAL STUDIES ALSO HAVE DEMONSTRATED VALPROATE INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

PRECAUTIONS

Hepatic Dysfunction: See BOXED WARNING, CONTRAINDICATIONS AND WARNINGS.

General: Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (eg, low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. Asymptomatic elevations of ammonia are more common and when present require more frequent monitoring. If clinically significant symptoms occur, DEPAKOTE therapy should be modified or discontinued.

Since valproate may interact with concurrently administered antiepileptic drugs, periodic plasma concentration determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See DRUG INTERACTIONS).

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Information for Patients. Since DEPAKOTE products may produce CNS depression, especially when combined CNS depressants (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

The specially coated particles in DEPAKOTE Sprinkle capsules have been observed in the stool, but this occurrence has not been associated with clinically significant effects.

Drug Interactions: Valproate may potentiate the action of CNS depressants (ie, alcohol, benzodiazepines, etc).

The concomitant administration of valproate with drugs that exhibit extensive protein binding (eg, aspirin, carbamazepine, dicumarol, and phenytoin) may result in alteration of serum drug concentrations.

There is evidence that valproate can cause an increase in serum phenobarbital concentrations by impairment of nonrenal clearance. This phenomenon can result in severe CNS depression. The combination of valproate and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone is metabolized to a barbiturate and, therefore, may also be involved in a similar or identical interaction.

There have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. Most reports have noted a decrease in total plasma phenytoin concentration. However, increases in total plasma phenytoin concentration, however, increases in total phenytoin serum concentration have been reported. An initial fall with subsequent increase in total phenytoin concentrations has also been reported. In addition, a decrease in total serum phenytoin with an increase in the free vs. protein bound phenytoin concentrations has been reported. The dosage of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide concentrations. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Caution is recommended when valproate is used with drugs affecting coagulation (eg, aspirin, warfarin). See ADVERSE REACTIONS.

Evidence suggests that there is an association between the use of certain antiepileptics and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing antiepileptics effectively lower plasma concentrations of the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. While valproate is not a significant enzyme inducer, and, therefore, would not be expected to decrease concentrations of steroid hormones, clinical data about the interaction of valproate with oral contraceptives is minimal.[2]

Carcinogenesis: Valproic acid was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 80, and 170 mg/kg/day for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis: Studies of valproate have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for valproate.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy: Pregnancy Category D: See WARNINGS.

Nursing Mothers: Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when divalproex sodium is administered to a nursing woman.

ADVERSE REACTIONS

Since divalproex sodium has usually been used with other antiepileptic drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to divalproex sodium alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.[3]

CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, and incoordination. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriate plasma levels; all patients recovered after the drug was withdrawn.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. A case of fatal epidermal necrolysis has been reported in a 6 month old infant taking valproate and several other concomitant medications.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation and frank hemorrhage (see PRECAUTIONS — *General* and *Drug Interactions*). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, and acute intermittent porphyria.

Hepatic: Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see WARNINGS).

Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea and parotid gland swelling. Abnormal thyroid function tests (see PRECAUTIONS).

Pancreatic: Acute pancreatitis, including fatalities.

Metabolic: Hyperammonemia (see PRECAUTIONS), hyponatremia, and inappropriate ADH secretion.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis.

Special Senses: Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established.

Other: Edema of the extremities, lupus erythematosus, and fever.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported.

The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution.

DOSAGE AND ADMINISTRATION

DEPAKOTE tablets and Sprinkle capsules are administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

Administration of Sprinkle Capsule: DEPAKOTE Sprinkle capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoonful) of soft food such as applesauce or pudding. The drug/food mixture should be swallowed immediately (avoid chewing) and not stored for future use. Each capsule is oversized to allow ease of opening.

Conversion from DEPAKENE to DEPAKOTE: In patients previously receiving DEPAKENE (valproic acid) therapy, DEPAKOTE products should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on a DEPAKOTE product, a dosing schedule of two or three times a day may be elected in selected patients.[4]

DEPAKOTE products provide equal extents of absorption, although they may not produce identical trough and peak valproate concentrations. DEPAKOTE tablets produce slightly higher peak concentrations than DEPAKOTE Sprinkle capsules. Such differences in the maximum and minimum valproate plasma concentrations are unlikely to be of clinical significance; however, changes in dosage administration of valproate or concomitant medications should be accompanied by increased monitoring of plasma concentrations of valproate and other medications, as well as the patient's clinical status.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum concentration and therapeutic effect. However, therapeutic valproate serum concentrations for most patients will range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY).

As the DEPAKOTE dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

HOW SUPPLIED

DEPAKOTE Sprinkle capsules (divalproex sodium coated particles in capsules), 125 mg, are white opaque and blue, and are supplied in bottles of 100 (NDC 0074-6114-13) and Abbo-Pac® unit dose packages of 100 (NDC 0074-6114-11).

DEPAKOTE tablets (divalproex sodium delayed-release tablets) are supplied as:

125 mg salmon pink-colored tablets:	
Bottles of 100	(NDC 0074-6212-13)
Abbo-Pac® unit dose packages of 100	(NDC 0074-6212-11)
250 mg peach-colored tablets:	
Bottles of 100	(NDC 0074-6214-13)
Bottles of 500	(NDC 0074-6214-53)
Abbo-Pac® unit dose packages of 100	(NDC 0074-6214-11)
500 mg lavender-colored tablets:	
Bottles of 100	(NDC 0074-6215-13)
Bottles of 500	(NDC 0074-6215-53)
Abbo-Pac® unit dose packages of 100	(NDC 0074-6215-11)

Recommended Storage: Store tablets below 86°F (30°C).
Store capsules below 77°F (25°C).

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Revised: February, 1992

Caution — Federal (USA) Law prohibits dispensing without prescription.

Original Contribution

Increased Metallothionein in the Liver and Kidney of Patients With Amyotrophic Lateral Sclerosis

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• To evaluate the putative role of metals and trace elements in the pathogenesis of classic amyotrophic lateral sclerosis, we studied the metallothionein levels in liver and kidney samples obtained at autopsy from 24 patients with amyotrophic lateral sclerosis and 18 controls. To assay metallothioneins and copper, cadmium, and zinc bound to metallothioneins, we used high-performance liquid chromatography directly coupled to flame atomic absorption spectrometry. Total cadmium, zinc, and copper concentrations were determined separately with the use of graphite furnace atomic absorption spectrometry with Zeeman background correction. The median liver metallothionein level was 60.3 mg/kg (range, 9 to 318 mg/kg) in the patients with amyotrophic lateral sclerosis and 12.6 mg/kg (range, 0 to 104.5 mg/kg) in the controls. In the kidney, median metallothionein levels were 126.9 mg/kg (range, 44 to 387 mg/kg) in the patients with amyotrophic lateral sclerosis and 64 mg/kg (range, 13.1 to 187 mg/kg) in the controls. Total zinc, cadmium, and copper concentrations, as measured by atomic absorption spectrometry, were not significantly different in patients vs controls. Our finding of elevated metallothionein levels in organs from patients with amyotrophic lateral sclerosis may indicate an increased exposure to metals.

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It has been hypothesized that classic amyotrophic lateral sclerosis (ALS) is caused by an environmental factor.[1-3] The possibility of putative involvement of toxic metals and trace elements has the longest history and is based on epidemiologic considerations[4] and an increasing number of case reports of ALS-like syndromes associated with long-term exposure to metals, particularly to lead[5] and mercury.[5] Metals and trace elements have been studied extensively in patients with ALS. Reported metal disturbances comprise increased spinal cord lead,[6] selenium,[7] and manganese[7,8] levels; increased cerebrospinal fluid lead levels[9]; and increased 24-hour urinary excretion of lead after edetic acid (EDTA) treatment.[10] However, most of these alterations could not be reproduced.[5] Conflicting results, difficulties in obtaining uncontaminated samples, and lack of history of exposure in most patients with ALS have led to skepticism concerning the exposure to metal hypothesis.

Metallothioneins (MTs) are major metal-binding proteins. Their proposed functions include the detoxification and storage of heavy metals.[11] Metallothioneins are a group of nonenzymatic, low-molecular-weight (6500 d) proteins. Sulfur-containing cysteine represents about one third of the amino acids that make up MTs. Metallothioneins bind with a decreasing order of avidity to copper, cadmium, and zinc ions. Transcription of MTs is induced by a wide variety of metal ions, hormones, and various pathophysiologic conditions associated with the acute-phase response.[11] Much less is known about the degradation of MTs, which is thought to take place mainly in the lysosomes.[12]

To establish a possible role of MTs in ALS, we have studied the hepatic and renal levels of MT, zinc, cadmium, and copper in liver and kidney samples obtained at autopsy from patients with classic ALS and controls.

PATIENTS, SUBJECTS, AND METHODS

At autopsy, 18 liver and 24 kidney samples were prospectively collected from 25 patients with classic ALS and 18 liver and 18 kidney samples were obtained from 19 sex- and age-matched controls. Seventeen patients with ALS had participated in an open clinical trial of *N*-acetyl-L-cysteine (NAC) in which high-dose NAC was administered subcutaneously daily. Eight patients had received NAC almost until the time of death, while the other nine had stopped taking NAC more than 3 months before death. In the eight patients, the median daily dose was 3.25 g (range, 1 to 5 g) for a median period of 13.5 months (range, 3 days to 26 months). The death-to-autopsy interval was less than 16 hours. No significant relationship has been found to exist between the death-to-autopsy interval and the concentrations of cadmium, zinc, copper, and MT.[13] Samples were stored in aluminum containers at −80°C until assay.

To simultaneously measure MT and MT-bound copper, cadmium and zinc, we applied protein separation by high-performance liquid chromatography, with on-line combined diode array detection and flame atomic absorption spectrometry.[14] Liver and kidney samples weighing 2 g were homogenized in

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Table 1.—Liver Metallothionein (MT), Zinc, MT-Zinc, Cadmium, MT-Cadmium, Copper, and MT-Copper Concentrations*

Group	ALS	Control	*P*
No.	18	18	
Age, y	66 (41-75)	69 (15-90)	.07
Sex, M/F	9/9	9/9	
MT	60.3 (9-318)	12.6 (0-104)	.002
Zinc	62.6 (37.8-272.5)	48.4 (27.6-99.1)	.06
MT-zinc	3.3 (0.5-29.8)	0.8 (0-8.4)	.004
Cadmium	2.6 (0.4-9.1)	1.8 (0.1-6)	.9
MT-cadmium	0.8 (0-3.1)	0.3 (0-1.5)	.007
Copper	4.5 (1-14.4)	4.3 (1.4-10.6)	.95
MT-copper	0.7 (0.2-1.7)	0.2 (0-1.5)	.0007

*Metals and MTs are expressed in milligrams per kilogram of wet weight. MT-zinc, MT-cadmium, and MT-copper denote the respective metal concentrations bound to MT. Values are expressed as median (reference range).

Table 2.—Kidney Metallothionein (MT), Zinc, MT-Zinc, Cadmium, MT-Cadmium, Copper, and MT-Copper Concentrations*

Group	ALS	Control	*P*
No.	24	18	
Age, y	66 (41-77)	69 (15-90)	.17
Sex, M/F	12/12	9/9	
MT	126.9 (44-387)	64 (13.1-187)	.003
Zinc†	26.8 (15.9-89)	24.9 (9.1-48.3)	.4
MT-zinc	1.9 (0.5-15)	0.6 (0.1-4.8)	.009
Cadmium†	21.9 (1.8-49)	14.9 (1.3-48.4)	.16
MT-cadmium	7.6 (1.3-26.5)	3.6 (0.7-13.1)	.003
Copper†	1.8 (0.5-7.5)	1.9 (0-9.5)	.9
MT-copper	0.8 (0.3-1.7)	0.4 (0-0.8)	<.001

*Metals and MTs are expressed in milligrams per kilogram of wet weight. MT-zinc, MT-cadmium, and MT-copper denote the respective metal concentrations bound to MT. Values are expressed as median (reference range).

†Two kidney samples from patients with amyotrophic lateral sclerosis were not sufficient for separate total metal analysis by atomic absorption spectrometry. Median and range are determined for 22 samples.

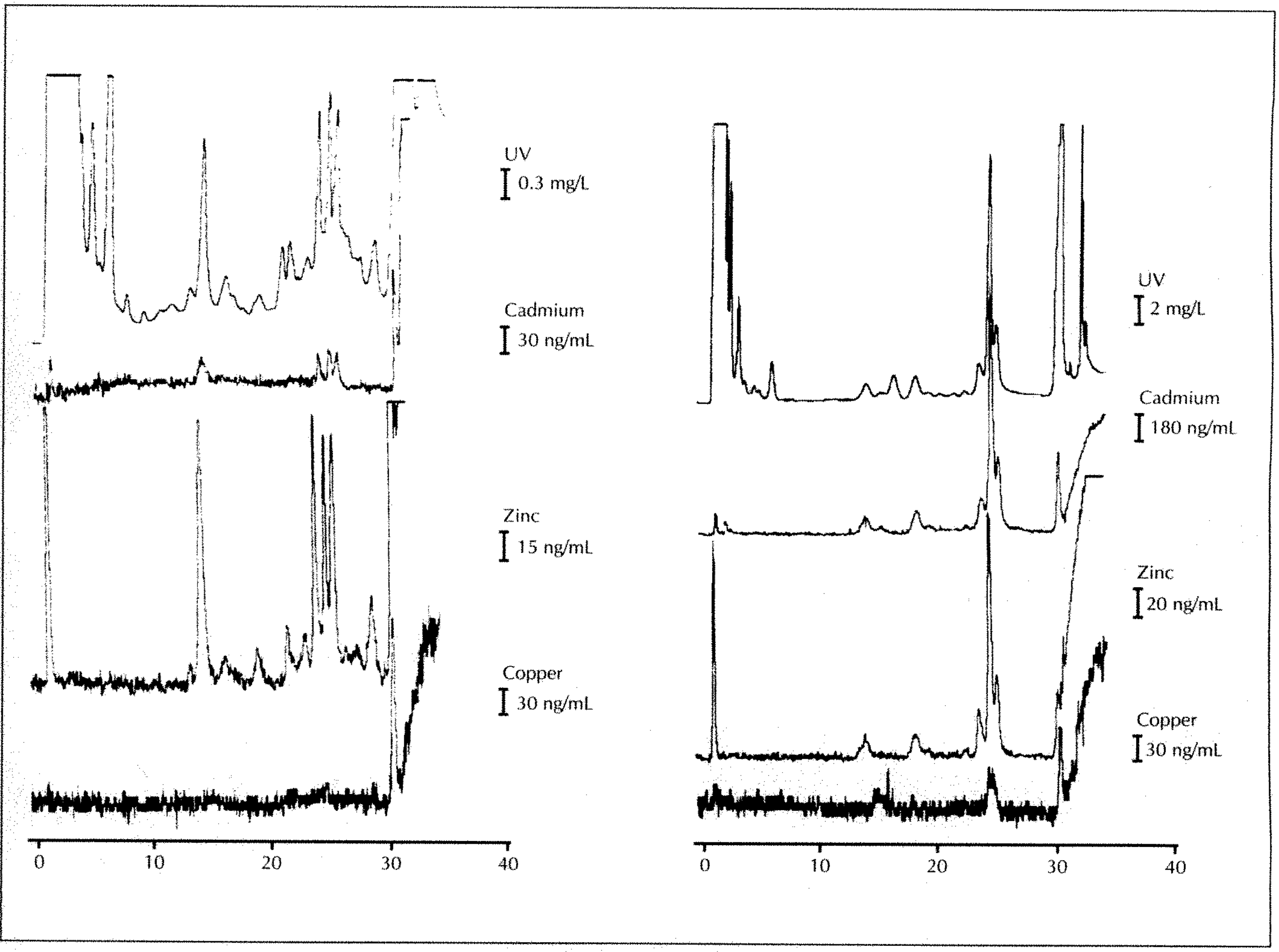

Fig 1.—*Chromatograms of metallothionein and protein-bound zinc, cadmium, and copper in liver (left) and kidney (right) specimens from a patient with amyotrophic lateral sclerosis. Metallothioneins elute between 23 and 27 minutes.*

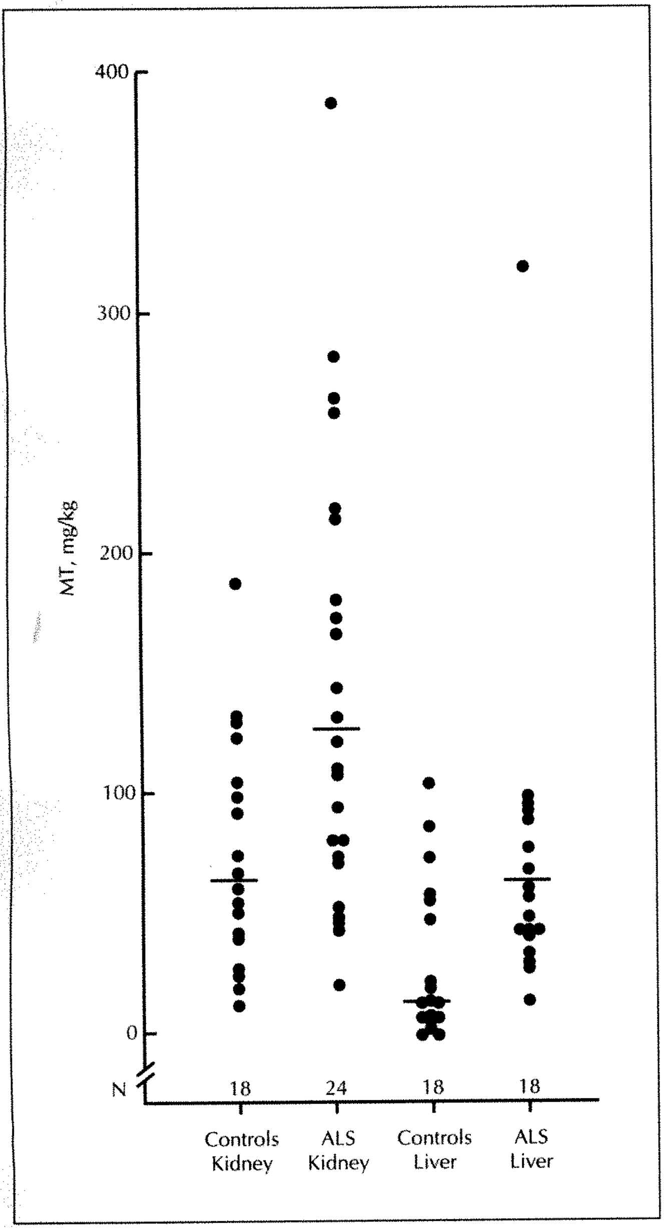

Fig 2.—*Levels of metallothionein (MT) in liver and kidney specimens from patients with amyotrophic lateral sclerosis and controls. Horizontal bars indicate the medians.*

10 mmol/L of ammoniumdihydrogenphosphate (pH 8.2), heated for 2 minutes at 100°C, and centrifuged for 90 minutes at 100 000*g* and 4°C. The resulting liver and kidney supernatants were filtered through 0.8-μm and 0.45-μm polymer filters (Millipore, Etten-Leur, the Netherlands), respectively. Appropriate amounts (0.2 to 1 mL) were injected into a reversed-phase Polymer Laboratories Reversed Phase-S high-performance liquid chromatography column (PLRP-S, Polymer Laboratories, Church Stretton, United Kingdom) and eluted with a gradient of 10 mmol/L of ammoniumdihydrogenphosphate (pH 8.2) and acetonitrile. Protein concentration was measured by diode array detection at 245 nm, and zinc, cadmium, and copper concentrations were measured by flame atomic absorption spectrometry at 213.9, 228.8, and 324.8 nm, respectively.

Total cadmium, zinc, and copper concentrations in liver and kidney samples were determined separately with the use graphite furnace atomic absorption spectrometry with Zeeman background correction.[15]

Group data are given as median and ranges. Differences between grouped data were assessed with the Mann-Whitney *U* test. A two-tailed level of $P<.05$ was considered statistically significant.

RESULTS

There were no significant differences in age and sex distribution between the patients with ALS and controls (Tables 1 and 2). The immediate causes of death in the ALS group were respiratory insufficiency (n=21), cardiac infarction (n=3), and sepsis (n=1) and in the control group were cardiac infarction (n=6), congestive heart failure (n=3), pneumonia (n=3), intracerebral hemorrhage (n=2), hypoxia (n=2), ovarian carcinoma (n=1), septic shock (n=1), and bleeding after aortic valve replacement (n=1).

Representative chromatograms of MT and MT-bound metals in liver and kidney are shown in Fig 1. Based on literature data and analysis of commercially available purified MT standards, the MTs elute between 23 and 27 minutes.[14]

In patients with ALS, the liver and kidney concentrations of MTs were significantly higher than in controls (Fig 2), as were the levels of zinc, cadmium, and copper bound to MT (Tables 1 and 2). In contrast, the total concentrations of zinc, cadmium, and copper in patients with ALS did not differ significantly from those in controls.

Nothing is known about the effect of NAC on MT levels. However, MT is rich in cysteine, and we compared MT concentrations in the eight patients who had received NAC almost until the time of death with those in the other patients with ALS, who had never taken NAC or who had stopped taking it more than 3 months before death. Liver MT concentrations in NAC-treated patients with ALS were 70 mg/kg (range, 40 to 93 mg/kg) and in non–NAC-treated patients were 54 mg/kg (range, 9 to 318 mg/kg) ($P>.7$). Kidney MT concentration was 155 mg/kg (range, 46 to 264 mg/kg) and 115 mg/kg (range, 44 to 387 mg/kg) in NAC-treated and non–NAC-treated patients with ALS, respectively ($P>.6$).

COMMENT

Our finding of elevated MT levels in liver and kidney specimens from patients with ALS may indicate either increased synthesis or decreased breakdown of these proteins. Ions of zinc, cadmium, and copper are potent inducers of MT synthesis.[11] The normal tissue levels of cadmium and copper (Tables 1 and 2) indicate that MTs have not been induced by a local excess of these metals. Liver zinc levels in patients with ALS are very close to being significantly higher than those in controls ($P=.06$). It is possible that a small difference in (long-term) exposure to zinc has resulted in increased liver and kidney MT concentrations. A number of other metals may be responsible for the increased MT levels in patients with ALS: mercury, manganese, and lead have been implicated in the etiology of ALS[5] and are able to induce MT[11] as well. Aluminum, much discussed in cases of ALS in the western Pacific region, has not been studied well in tissues from patients with classic ALS.[5] According to one report, aluminum can induce and bind to MT.[16] However, this finding was not confirmed by other reports,[17] and aluminum is not generally regarded as an inductor of MT.[11]

Metallothionein levels could have increased due to overproduction of defective proteins. Although this issue was not addressed in our study, the normal percentage of

MT bound to zinc, cadmium, and copper in patients with ALS defied this notion.

Synthesis of MTs, which are rich in cysteine, could hypothetically be induced by NAC, which had been taken by eight patients with ALS until the time of death. No significant differences in MT levels were found between patients with ALS who did and did not receive NAC treatment. Many other factors are known to induce MT synthesis in animal models and cultured cells.[11] Because much less is known about MT induction in humans, it is difficult to discern potentially confounding factors between patients with ALS and controls. It is possible that low-grade differences in MT-inducing agents (known or unknown) have existed for a prolonged period before death. Wasting and weight loss are prominent features in most patients with terminal ALS. Starvation is known to induce MT synthesis in rats[18]; however, the patients in the study of Lui et al[13] on Alzheimer's disease retained normal liver MT levels despite severe weight loss.

Sulfoxidation is impeded in ALS.[3] It is unknown whether the breakdown of MTs, which are rich in the sulfur-containing cysteine, requires sulfoxidation. Decreased sulfoxidation does not seem to lead necessarily to an increase in MT, as in Alzheimer's disease hepatic MT levels are normal[13] despite disturbed sulfoxidation.[19]

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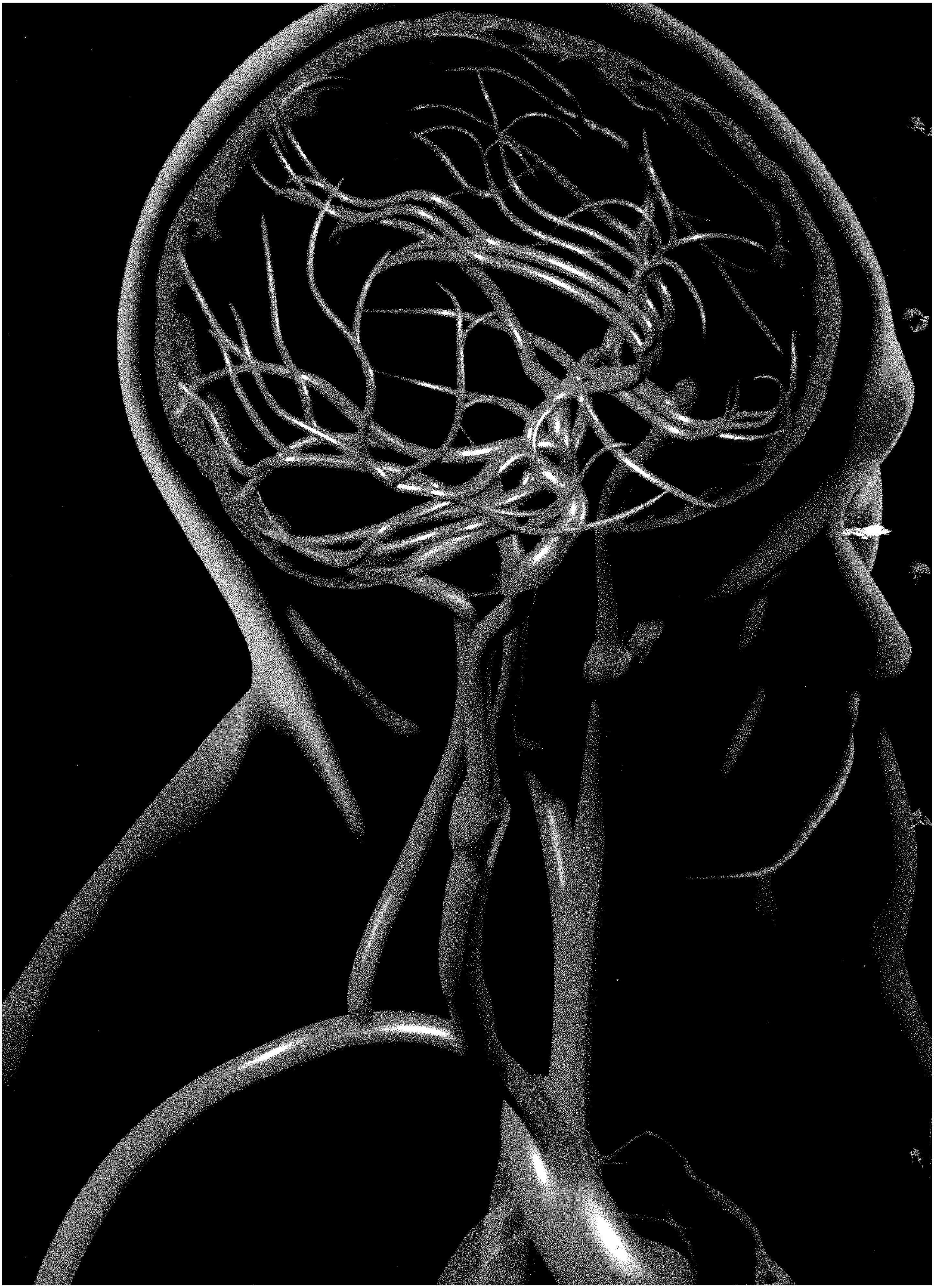

Introducing the First Prescription Antiplatelet Agent that Significantly Reduces the Risk of Stroke[1,2]

Ticlid®

Ticlopidine HCl 250mg Tablets bid

Clinical Trials Demonstrated:

48% reduction vs aspirin[3] in risk of initial stroke in TIA* patients at year 1 (*P* = .0004, n = 3034), the year of greatest risk

33% reduction in risk[2,4] of fatal or nonfatal recurrent stroke at year 1 (*P* = .008, n = 1053), the year of greatest risk

Proven effective in women as well as men[1,2,3,4]

Indications

Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life threatening (see Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke

TICLID, therefore, is appropriate first-line therapy for reducing the risk of thrombotic stroke in:
— all female TIA patients
— all males at risk for recurrent stroke
— all females at risk for recurrent stroke
— all aspirin-intolerant male TIA patients

Side Effects

In clinical trials, neutropenia† occurred in a total of 2.4% of patients (0.8% severe‡) and was not typically associated with clinical signs or symptoms

Therefore, CBC monitoring (including differentials) for neutropenia is essential every 2 weeks for the first 3 months of therapy

The most frequently occurring side effects involved the GI tract: diarrhea (12.5%), nausea (7.0%), dyspepsia (7.0%); rash also occurred (5.1%)

Although most side effects were mild, 21% of patients discontinued therapy due to an adverse event in clinical trials

*Analysis based on all study participants, which included patients with transient ischemic attack, transient monocular blindness, reversible ischemic neurological deficit, and minor stroke.
†Defined as <1200 neutrophils/mm^3, seen in 50/2048 patients
‡Defined as <450 neutrophils/mm^3, seen in 17/2048 patients

SYNTEX

1. Hass WK, Easton JD, Adams HP Jr et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med.* 1989;321(8):501-507. 2. Gent M, Easton JD, Hachinski VC et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet.* 1989;1:1215-1220. 3. TICLID (ticlopidine HCl) tablets full prescribing information. 4. Biller J, Love BB, Gordon DL. Antithrombotic therapy for ischemic cerebrovascular disease. *Semin Neurol.* 1991;11(4):353-367.

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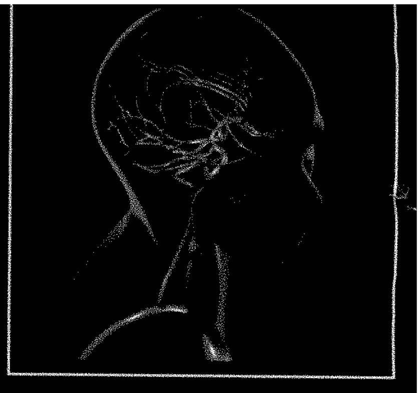

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INDICATIONS AND USAGE TICLID is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because TICLID is associated with a risk of neutropenia/agranulocytosis, which may be life-threatening (See Warnings), TICLID should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke. **CONTRAINDICATIONS** The use of TICLID® is contraindicated in the following conditions: Hypersensitivity to the drug. Presence of hematopoietic disorders such as neutropenia and thrombocytopenia. Presence of a hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding). Patients with severe liver impairment.

WARNINGS

Neutropenia

Neutropenia defined in these studies as an ANC <1200 neutrophils/mm^3 occurred in 50 of 2,048 (2.4%) stroke patients who received TICLID in clinical trials. *Severe Neutropenia (<450 neutrophils/mm^3):* Severe neutropenia and/or agranulocytosis occurred in 17 of the 2,048 (0.8%) patients who received TICLID. When the drug was discontinued in these patients, the neutrophil counts returned to normal (>1200 neutrophils/mm^3) within 1-3 weeks. *Mild to Moderate Neutropenia (451-1200 neutrophils/mm^3):* Mild to moderate neutropenia occurred in 33 of the 2,048 (1.6%) patients who received TICLID. Eleven of the patients discontinued treatment and recovered within a few days. In the remaining 22 patients, the neutropenia was transient and did not require discontinuation of therapy. The onset of severe neutropenia occurred 3 weeks to 3 months after the start of therapy with TICLID, with no documented cases of severe neutropenia beyond that time in the large controlled trials. The bone marrow typically showed a reduction in myeloid precursors. It is therefore essential that CBCs and white cell differentials be performed every two weeks starting from the second week to the end of the third month of therapy with TICLID, but more frequent monitoring is necessary for patients whose absolute neutrophil counts have been consistently declining or are 30% less than the baseline count. Neutropenia (an absolute neutrophil count (ANC) of less than 1200 neutrophils/mm^3) is calculated as follows: ANC = WBC × % neutrophils. If clinical evaluation and repeat laboratory testing confirm the presence of neutropenia (<1200/mm^3), the drug should be discontinued. In clinical trials, when therapy was discontinued immediately upon detection of neutropenia, the neutrophil counts returned to normal within 1-3 weeks. After the first three months of therapy, CBCs need be obtained only for patients with signs or symptoms suggestive of infection.

Thrombocytopenia Rarely, thrombocytopenia may occur in isolation or together with neutropenia. If clinical evaluation and repeat laboratory testing confirm the presence of thrombocytopenia (<80,000 cells/mm^3), the drug should be discontinued. Cholesterol Elevation TICLID® therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8-10% within one month of therapy and persist at that level. The ratios of the lipoprotein subfractions are unchanged. **Other Hematological Effects** Rare cases of pancytopenia and thrombotic thrombocytopenic purpura, some of which have been fatal, have been reported in Post-Marketing Surveillance. **Anticoagulant Drugs** The tolerance and safety of coadministration of TICLID with heparin, oral anticoagulants, or fibrinolytic agents has not been established. If a patient is switched from an anticoagulant or fibrinolytic drug to TICLID, the former drug should be discontinued prior to TICLID administration. **PRECAUTIONS General** TICLID should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or pathological conditions. If it is desired to eliminate the antiplatelet effects of TICLID prior to elective surgery, the drug should be discontinued 10-14 days prior to surgery. Several controlled clinical studies have found increased surgical blood loss in patients undergoing surgery during treatment with ticlopidine. In TASS and CATS it was recommended that patients have ticlopidine discontinued prior to elective surgery. Several hundred patients underwent surgery during the trials, and no excessive surgical bleeding was reported. Prolonged bleeding time is normalized within two hours after administration of 20 mg methylprednisolone i.v. Platelet transfusions may also be used to reverse the effect of TICLID on bleeding. **GI Bleeding** TICLID prolongs template bleeding time. The drug should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients on TICLID. (See Contraindications.) **Use in Hepatically Impaired Patients** Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of TICLID is not recommended in this population. (See Clinical Pharmacology and Contraindications.) **Use in Renally Impaired Patients** There is limited experience in patients with renal impairment. In controlled clinical trials, no unexpected problems have been encountered in patients having mild renal impairment and there is no experience with dosage adjustment in patients with greater degrees of renal impairment. Nevertheless, for renally impaired patients it may be necessary to reduce the dosage of ticlopidine or discontinue it altogether, if hemorrhagic or hematopoietic problems are encountered. (See Clinical Pharmacology) **Information for the Patient (See PPI)** Patients should be told that a decrease in the number of white blood cells (neutropenia) can occur with TICLID®, especially during the first three months of treatment, and that if neutropenia is severe, it could result in an increased risk of infection. They should be told it is critically important to obtain the scheduled blood tests to detect neutropenia. Patients should also be reminded to contact their physicians if they experience any indication of infection such as fever, chills, and sore throat, all of which may be consequences of neutropenia. All patients should be told that it may take them longer than usual to stop bleeding when they take TICLID and that they should report any unusual bleeding to their physician. Patients should tell physicians and dentists that they are taking TICLID before any surgery is scheduled and before any new drug is prescribed. Patients should be told to report promptly side effects of TICLID such as severe or persistent diarrhea, skin rashes, or subcutaneous bleeding, or any signs of cholestasis, such as yellow skin or sclera, dark urine, or light colored stools. Patients should be told to take TICLID with food or just after eating in order to minimize gastrointestinal discomfort. **Laboratory Tests** *Liver Function:* TICLID therapy has been associated with elevations of alkaline phosphatase and transaminases which generally occurred within 1-4 months of therapy initiation. In controlled clinical trials, the incidence of elevated alkaline phosphatase (greater than 2 times upper limit of normal) was 7.6% in ticlopidine patients, 6.0% in placebo patients and 2.5% in aspirin patients. The incidence of elevated AST (SGOT) (greater than 2 times upper limit of normal) was 3.1% in ticlopidine patients, 4.0% in placebo patients and 2.1% in aspirin patients. No progressive increases were observed in closely monitored clinical trials (e.g. no transaminase greater than 10 times the upper limit of normal was seen), but most patients with these abnormalities had therapy discontinued. Occasionally patients had developed minor elevations in bilirubin. Based on post-marketing and clinical trials experiences, liver function testing should be considered whenever liver dysfunction is suspected, particularly during the first four months of treatment. **Drug Interactions** Therapeutic doses of TICLID caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios, or being given to patients with hepatic impairment, may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine. Studies of specific drug interactions yielded the following results. ***Aspirin:*** Aspirin did not modify the ticlopidine-mediated inhibition of ADP-induced platelet aggregation, but ticlopidine potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of this combination has not been established and concomitant use of aspirin and ticlopidine is not recommended. (See Precautions – GI Bleeding). ***Antacids:*** Administration of TICLID after antacids resulted in an 18% decrease in plasma levels of ticlopidine. ***Cimetidine:*** Chronic administration of cimetidine reduced the clearance of a single dose of TICLID by 50%. ***Digoxin:*** Co-administration of TICLID with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected. ***Theophylline:*** In normal volunteers, concomitant administration of TICLID resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hr and a comparable reduction in total plasma clearance of theophylline. ***Phenobarbital:*** In six normal volunteers, the inhibitory effects of TICLID on platelet aggregation were not altered by chronic administration of phenobarbital. ***Phenytoin:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID and it may be useful to remeasure phenytoin blood concentrations. ***Propranolol:*** In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with TICLID.

℞

TICLID 250 mg
#30
Sig: 1 Tab bid
with meals

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, TICLID was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs without evidence of clinically significant adverse interactions. (See Precautions.) **Food Interaction:** The oral bioavailability of ticlopidine is increased by 20% when taken after a meal. Administration of TICLID with food is recommended to maximize gastrointestinal tolerance. In controlled trials, TICLID was taken with meals. **Carcinogenesis, Mutagenesis, Impairment of Fertility** In a two-year oral carcinogenicity study in rats, ticlopidine at daily doses of up to 100 mg/kg (610 mg/m^2) was not tumorigenic. For a 70 kg person (1.73m^2 body surface area), the dose represents 14 times the recommended clinical dose on a mg/kg basis and 2 times the clinical dose on body surface area basis. In a 78 week oral carcinogenicity study in mice ticlopidine at daily doses up to 275 mg/kg (1180 mg/m^2) was not tumorigenic. The dose represents 40 times the recommended clinical dose on a mg/kg basis and 4 times the clinical dose on body surface area basis. Ticlopidine was not mutagenic in *in vitro* Ames test, rat hepatocyte DNA-repair assay, and Chinese hamster fibroblast chromosomal aberration test and *in vivo* mouse spermatozoid morphology test, Chinese hamster micronucleus test and Chinese hamster bone marrow cell sister chromatid exchange test. Ticlopidine was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day. **Pregnancy: Teratogenic Effects** Pregnancy Category B. Teratology studies have been conducted in mice (doses up to 200 mg/kg/day), rats (doses up to 400 mg/kg/day) and rabbits (doses up to 200 mg/kg/day). Doses of 400 mg/kg in rats, 200 mg/kg/day in mice, and 100 mg/kg in rabbits produced maternal toxicity as well as fetal toxicity, but there was no evidence of a teratogenic potential of ticlopidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers** Studies in rats have shown ticlopidine is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ticlopidine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** Safety and efficacy in patients under the age of 18 have not been established. **Geriatric Use** Clearance of ticlopidine is somewhat lower in elderly patients and trough levels are increased. The major clinical trials with TICLID were conducted in an elderly population with an average age of 64 years. Of the total number of patients in the therapeutic trials, 45% of patients were over 65 years old and 12% were over 75 years old. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse reactions were relatively frequent, with over 50% of patients reporting at least one. Most (30 to 40%) involved the gastrointestinal tract. Most adverse effects are mild, but 21% of patients discontinued therapy because of an adverse event, principally diarrhea, rash, nausea, vomiting, G.I. pain, and neutropenia. Most adverse effects occur early in the course of treatment, but a new onset of adverse effects can occur after several months. The incidence rates of adverse events listed in the following table were derived from multicenter, controlled clinical trials described above comparing TICLID, placebo, and aspirin over study periods of up to 5.8 years. Adverse events considered by the investigator to be probably drug-related that occurred in at least one percent of patients treated with TICLID are shown in the following table:

Percent of Patients with Adverse Events in Controlled Studies

Event	TICLID (n = 2048) Incidence	Aspirin (n = 1527) Incidence	Placebo (n = 536) Incidence
Any Events	*60.0 (20.9)*	*53.2 (14.5)*	*34.3 (6.1)*
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	1.7 (0.9)
Dyspepsia	7.0 (1.1)	9.0 (2.0)	0.9 (0.2)
Rash	5.1 (3.4)	1.5 (0.8)	0.6 (0.9)
GI Pain	3.7 (1.9)	5.6 (2.7)	1.3 (0.4)
Neutropenia	2.4 (1.3)	0.8 (0.1)	1.1 (0.4)
Purpura	2.2 (0.2)	1.6 (0.1)	0.0 (0.0)
Vomiting	1.9 (1.4)	1.4 (0.9)	0.9 (0.4)
Flatulence	1.5 (0.1)	1.4 (0.3)	0.0 (0.0)
Pruritus	1.3 (0.8)	0.3 (0.1)	0.0 (0.0)
Dizziness	1.1 (0.4)	0.5 (0.4)	0.0 (0.0)
Anorexia	1.0 (0.4)	0.5 (0.3)	0.0 (0.0)
Abnormal Liver Function test	1.0 (0.7)	0.3 (0.3)	0.0 (0.0)

Incidence of discontinuation, regardless of relationship therapy, is shown in parentheses.

Neutropenia/Thrombocytopenia See Warnings. **Gastrointestinal** TICLID therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and typically are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. **Hemorrhagic** TICLID has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding and perioperative bleeding. Intracerebral bleeding was rare in clinical trials with TICLID, with an incidence no greater than that seen with comparator agents. (Ticlopidine 0.5%, aspirin 0.6%, placebo 0.75%.) **Rash** Ticlopidine has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean onset time of 11 days. If drug is discontinued, recovery occurs within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of severe rashes. **Less Frequent Adverse Reactions (Probably Related)** Clinical adverse experiences occurring in 0.5 to 1.0 percent of patients in the controlled trials include: Digestive System: GI fullness. Skin and Appendages: urticaria. Nervous System: headache. Body as a Whole: asthenia, pain. Hemostatic System: epistaxis. Special Senses: tinnitus. In addition, rarer, relatively serious events have also been reported, mainly from foreign post marketing experience: Pancytopenia, hemolytic anemia with reticulocytosis, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, cholestatic jaundice, nephrotic syndrome, myositis, hyponatremia, immune thrombocytopenia and thrombocytopenic thrombotic purpura (TTP). **OVERDOSAGE** One case of deliberate overdosage with TICLID has been reported by foreign postmarketing surveillance program. A 38 year old male took a single 6000 mg dose of TICLID (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Single oral doses of ticlopidine at 1600 mg/kg and 500 mg/kg were lethal to rats and mice, respectively. Symptoms of acute toxicity were GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and abnormal gait. **DOSAGE AND ADMINISTRATION** The recommended dose of TICLID is 250 mg BID taken with food. Other doses have not been studied in controlled trials for these indications.

SYNTEX
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U.S. Patent Nos. 4,051,141; 4,591,592
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Original Contribution

Local Cerebral Blood Flow and Its Response to Intravenous Levodopa in Progressive Supranuclear Palsy

Comparison With Parkinson's Disease

Masahiro Kobari, MD; Yasuo Fukuuchi, MD; Tamotsu Shinohara, MD; Shigeru Nogawa, MD; Kazushi Takahashi, MD

• The local cerebral blood flow (LCBF) at steady state and after the intravenous administration of levodopa (1 mg/kg) was measured by the xenon-enhanced computed tomographic method in six patients with progressive supranuclear palsy (PSP) and in nine patients with idiopathic Parkinson's disease. The baseline LCBF values in most brain regions in patients with PSP were lower than those in patients with Parkinson's disease, and hyperfrontality of the LCBF was lost. In patients with Parkinson's disease, the injection of levodopa markedly increased LCBF, especially in the striatum, thalamus, and internal capsule (approximately 40%). In patients with PSP, however, levodopa did not increase the LCBF in all brain regions examined. The LCBF increases after the administration of levodopa in patients with Parkinson's disease may be secondary to metabolic activation of the dopaminergic system. The different LCBF responses to levodopa between patients with PSP and those with Parkinson's disease may reflect differences in pathologic features, such as in the degree of preservation of nigrostriatal dopaminergic neurons and the distribution and density of dopamine receptors, and are also related to the clinical effectiveness of levodopa therapy.

(*Arch Neurol.* 1992;49:725-730)

Progressive supranuclear palsy (PSP), as reported by Steele et al[1] in 1964, is characterized by vertical gaze palsy, pseudobulbar palsy, nuchal dystonia, and dementia. Although patients with PSP exhibit signs and symptoms similar to those of Parkinson's disease, it has been regarded as a definitive entity from both clinical and neuropathologic viewpoints.[2,3] The benefits of oral levodopa therapy in PSP are very limited,[3,4] while it is effective in the treatment of idiopathic Parkinson's disease.

We sought to elucidate the cerebral hemodynamic characteristics of PSP compared with those of Parkinson's disease. We hypothesized that the clinical and pathophysiologic differences between the two diseases could be reflected in cerebral blood flow (CBF) measurements obtained before and after the administration of levodopa. First, the baseline CBF value was determined in patients with PSP and Parkinson's disease. Second, the CBF changes that occur in response to the intravenous administration of levodopa were compared between the two diseases. The local CBF (LCBF) was measured by the xenon-enhanced computed tomographic (CT) method,[5,6] which permits high-resolution, three-dimensional measurements of LCBF in the cerebral cortex as well as the subcortical gray and white matter.

PATIENTS AND METHODS

Patients

Six patients with PSP (four men and two women; mean [±SD] age, 65.5±5.6 years) and nine patients with idiopathic Parkinson's disease (three men and six women; mean age, 62.4±11.9 years) were evaluated. There was no statistically significant difference in mean age between the two groups.

The diagnosis of PSP was made clinically according to the criteria described by Jackson and colleagues.[4] The criteria require that all of the following features be present for a diagnosis of PSP: (1) an age at onset older than 50 years; (2) parkinsonian signs, including bradykinesia, postural or gait disorder, axial rigidity, and minimal or no tremor at rest; (3) pseudobulbar signs, including dysarthria, dysphagia, hyperactive gag reflex, and emotional incontinence; and (4) extraocular movement abnormalities characterized by supranuclear vertical gaze palsy, particularly downgaze paralysis. Table 1 summarizes the clinical features of the patients with PSP who were included in this study. All patients satisfied the above criteria. Furthermore, all patients had mild to moderate dementia. Cognitive function was evaluated by Hasegawa's dementia rating scale,[7] which is similar to the Mini-Mental State Examination. The duration of illness ranged from 0.6 to 9 years at the time of CBF measurements. In all but one of the patients, brain CT scans and/or magnetic resonance images revealed atrophy in the cerebral cortex or brain stem. Oral levodopa therapy was ineffective or only minimally effective in four of five patients in whom treatment was attempted.

The diagnosis of idiopathic Parkinson's disease was established according to the presence of the classic triad, ie, rigidity of the muscles, bradykinesia, and resting tremor (Table 2). To rule out secondary parkinsonism due to cerebrovascular disease or other degenerative diseases, patients with sensory disturbances, motor weakness, pyramidal tract signs, or cerebellar signs were excluded. Patients with focal lesions or definite cerebral atrophy on

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Table 1.—Clinical Features of Patients With Progressive Supranuclear Palsy*

Patient/ Age, y/Sex	Duration, y	Vertical Gaze Palsy	Pseudobulbar Palsy	Nuchal Dystonia	Parkinsonism	Dementia	CT/MRI Lesions	Response to Levodopa
1/73/F	9	++	+++	++	+++	+	++	±
2/64/M	8	+++	+++	+++	++−+++	++	++	±
3/57/M	1.7	++	+	+	++	+	+	Not used
4/70/M	2	+++	++	++	+++	++	+−++	−
5/66/F	0.6	+	+	+−++	++	+	−	+
6/63/M	2.1	++	+++	++	+++	+	++	−

*Triple plus sign indicates marked; double plus sign, moderate; single plus sign, mild; plus/minus sign, minimal; minus sign, absent; CT, computed tomographic; and MRI, magnetic resonance imaging.

Table 2.—Clinical Features of Patients With Parkinson's Disease*

Patient/ Age, y/Sex	Duration, y	Hoehn and Yahr Grade	Rigidity of Muscles	Bradykinesia	Resting Tremor	Gait Disturbance	CT/MRI Lesions	Response to Levodopa
1/69/M	3	3	++	+	±	++	−	++
2/74/F	11	4	++	+++	+++	+++	±	++
3/42/F	5	3	+++	++	+	++	−	+++
4/60/F	3.5	3	++	++	++	+−++	−	++
5/66/F	4	2	++	+	+++	±	−	+++
6/44/F	0.5	2	+	±	++	−	−	+++
7/71/F	9	3	++	+++	++	++−+++	−	+++
8/73/M	1.4	3	++	++	−	++	±	+
9/63/M	1	3	+	+−++	++	++	−	++

*See Table 1 for explanation of abbreviations and symbols.

brain CT scans and/or magnetic resonance images were also excluded. The duration of illness ranged from 0.5 to 11 years, and the severity ranged from grades 2 to 4, according to the classification of Hoehn and Yahr. In all cases, dementia was not clinically evident. Treatment with oral levodopa (including that with peripheral aromatic L-amino acid decarboxylase inhibitors) improved the parkinsonian symptoms and signs in all cases.

Methods

Local CBF was measured with the xenon-enhanced CT method,[5,6] in which biologically and radiologically inactive xenon gas is used as a tracer. The LCBF values were calculated by applying the in vivo autoradiographic technique, according to Kety's equation.[8,9] The xenon concentration in the local brain tissue was estimated by CT scanning (CT9200 or CT Vertex3000, GE Medical Systems, Milwaukee, Wis) of the brain, as the changes in xenon concentration of the local brain tissue parallel the changes in local CT numbers.

Informed consent was obtained from all patients before LCBF measurements were made. Patients were instructed to recline at rest on a CT table with both eyes closed. Levodopa therapy, if any, was discontinued for at least 5 days before the LCBF measurements were made. A thin catheter was inserted into the left brachial artery to monitor the systemic arterial blood pressure and to intermittently withdraw arterial blood samples. After a baseline 10-mm-thick CT scan was obtained at a level that included the frontal, temporal, and occipital portions of the cortex as well as the thalamus and basal ganglia, inhalation of 35% xenon gas with 65% oxygen was begun. After 3 minutes, a second CT scan at the same level was obtained, and the inhalation of xenon gas was terminated. Four-milliliter arterial blood samples were withdrawn at 15- to 30-second intervals during the inhalation of xenon gas.

Immediately after the first LCBF measurement was obtained, 1 mg/kg of levodopa (1-3,4-dihydroxyphenylalanine, Dopaston, Sankyo Co, Tokyo, Japan) with 50 mL of saline solution was infused intravenously within 30 minutes. During the last 3 minutes of levodopa infusion, the second LCBF measurement was performed with use of the same procedure as in the first measurement. To obtain the CT scan saturated with xenon, inhalation of xenon gas was continued for a total of 15 minutes during the second measurement, after which the CT scan at the same level was obtained. This image was used to estimate the brain-blood partition coefficients of the xenon gas for each CT pixel.

The withdrawn blood samples in the syringe were placed in a phantom simulating the human skull and brain tissue. The changes in xenon gas concentration in the arterial blood were estimated by scanning the serial blood samples in the syringe. Arterial blood samples were also subjected to analysis of blood gases (PaO_2 and $PaCO_2$) and pH level determination.

With the use of computer programs developed in our laboratory, the LCBF values for each of the CT pixels were calculated (by a personal computer, NEC Corporation, Tokyo) from the changes in xenon gas concentration in the brain and in the arterial blood plus the estimated partition coefficients of the xenon gas, according to the in vivo autoradiographic technique.[8,9] Each pixel represented $2.4 \times 2.4 \times 10$ mm^3 of brain tissue. An LCBF image was then reconstructed and superimposed on the CT scan. By cursoring over the cerebral region of interest on the CT scan displayed on the computer screen,[6] mean LCBF values for the following cerebral structures (average, 50 pixels) were automatically calculated: the frontal, temporal, and occipital cortex; the caudate nucleus; the putamen; the thalamus; the frontal and occipital white matter; and the internal capsule. All data are shown as the mean (±SD), unless otherwise stated. Statistical analysis was performed with Student's *t* test and the Wilcoxon Signed-Rank Test.

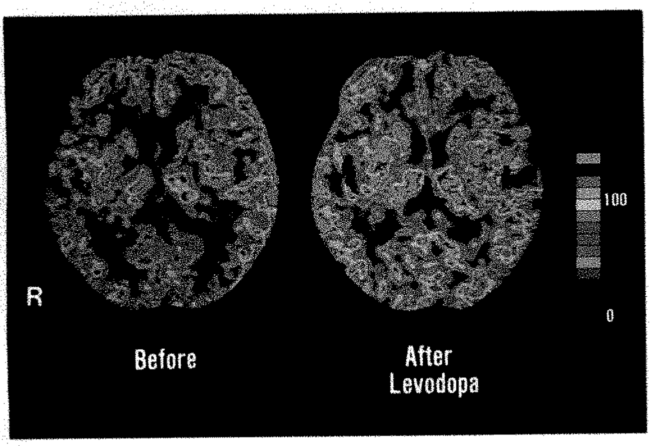

Fig 1.—*Local cerebral blood flow images obtained at the level of the basal ganglia in a 60-year-old woman with Parkinson's disease. The image obtained before the administration of levodopa (left) shows a mild but diffuse reduction in local cerebral blood flow. The pattern of local cerebral blood flow distribution is normal. The image obtained after levodopa administration (right) shows an increase in local cerebral blood flow in most of the cerebral regions, especially in the caudate nucleus, the putamen, and the thalamus. The left hemisphere is located on the right side of the image and vice versa.*

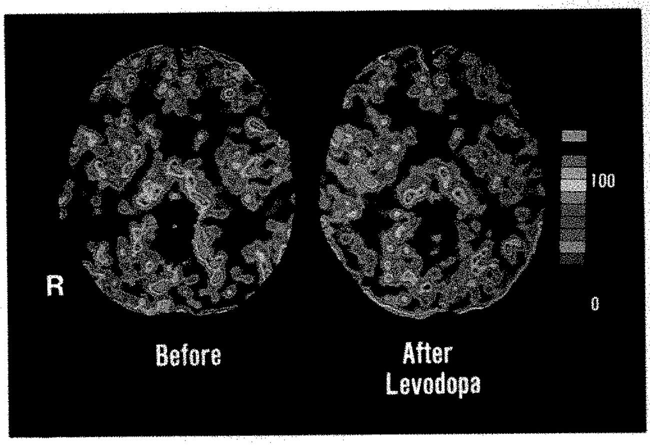

Fig 2.—*Local cerebral blood flow images obtained in a 66-year-old woman with progressive supranuclear palsy. The image obtained before the administration of levodopa (left) shows diffuse and marked local cerebral blood flow reductions, especially in the frontal lobe, compared with images of the patient with Parkinson's disease shown in Fig 1. The image obtained after the administration of levodopa (right) shows decreased local cerebral blood flow in some brain regions. The left hemisphere is located on the right side of the image and vice versa.*

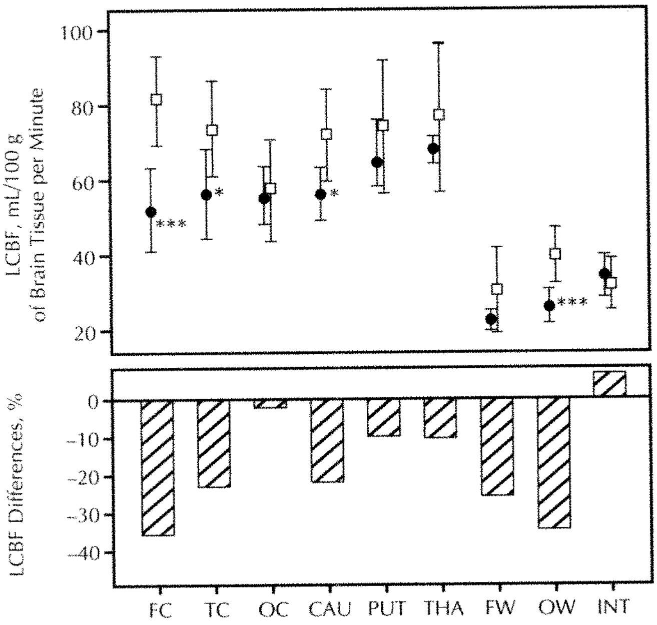

Fig 3.—*Top, Mean local cerebral blood flow (LCBF) values for nine cerebral regions in patients with Parkinson's disease (open squares; n=9) and patients with progressive supranuclear palsy (solid circles; n=6). Single asterisk indicates $P<.05$; triple asterisk, $P<.005$. Values are mean±SD. Bottom, Percent of LCBF difference in patients with progressive supranuclear palsy compared with that in patients with Parkinson's disease, calculated from the mean LCBF values in the graph shown at top. In the patients with progressive supranuclear palsy, the LCBF values in the cerebral cortex as well as the subcortical gray and white matter were all lower. In the cerebral cortex, the LCBF difference was most marked in the frontal cortex (FC). TC indicates temporal cortex; OC, occipital cortex; CAU, caudate nucleus; PUT, putamen; THA, thalamus; FW, frontal white matter; OW, occipital white matter; and INT, internal capsule.*

RESULTS

Figure 1 presents examples of the color-coded LCBF images obtained at the level of the basal ganglia in a 60-year-old woman with idiopathic Parkinson's disease. The LCBF pattern obtained while the patient was levodopa free (image shown on the left) is normal, except that the overall LCBF values are slightly decreased compared with those of healthy subjects of similar age. The LCBF image obtained after the intravenous administration of levodopa (image shown on the right) displays marked and widespread increases in LCBF, especially in such regions as the bilateral basal ganglia and thalamus.

Figure 2 presents examples of LCBF images obtained in a 66-year-old woman with PSP. The LCBF image obtained before the administration of levodopa (image shown on the left) displays a lower LCBF in most of the brain regions compared with the image obtained in the patient with Parkinson's disease that is depicted in Fig 1. After the administration of levodopa (image shown on the right), increases in LCBF similar to those recorded in the patient with Parkinson's disease were not observed in this patient with PSP.

The upper portion of Fig 3 summarizes the steady-state LCBF values for the nine cerebral regions in which LCBF values were measured before the administration of levodopa in the patients with Parkinson's disease (n=9) and PSP (n=6). In the patients with PSP, the LCBF values for most of the brain regions, including the cerebral cortex, white matter, and basal ganglia, were lower than those of the patients with Parkinson's disease. The lower portion of Fig 3 shows the percent differences in LCBF in the patients with PSP compared with those in patients with Parkinson's disease. In the patients with PSP, the LCBF value was approximately 35% lower in the frontal cortex ($P<.005$). The LCBF values in the temporal cortex ($P<.05$), caudate nucleus ($P<.05$), and occipital white matter ($P<.005$) were also significantly lower.

Table 3 summarizes the mean LCBF values for the nine brain regions before and after the administration of levodopa in patients with PSP (n=5) and those with Parkinson's disease (n=9). Figure 4 shows the percent changes of LCBF that occurred after the administration of levodopa in the two groups. There were no significant differences in PaCO_2 values before and after the injection of levodopa in the patients with PSP (37.7±3.2 and 38.3±3.4 mm Hg) and those with Parkinson's disease (38.0±4.2 and 37.9±4.7 mm

Table 3.—Local Cerebral Blood Flow Values Before and After the Intravenous Administration of Levodopa (1 mg/kg)*

	PSP (n=5)		Parkinson (n=9)	
	Before	**After**	**Before**	**After**
Cortex				
Frontal	53.1±12.1	53.6±18.3	80.5±12.0	94.1±10.9†
Temporal	58.6±10.4	57.8±14.0	72.3±13.5	82.7±19.5
Occipital	53.9±8.4	47.4±9.2	55.8±13.1	66.8±16.5
Caudate nucleus	53.4±6.5	49.2±20.6	70.5±12.3	97.3±9.5‡
Putamen	67.4±7.7	50.9±16.4	72.5±18.0	96.3±14.2§
Thalamus	66.4±3.6	57.1±18.1	74.4±20.4	100.3±10.0‡
White matter				
Frontal	20.2±2.9	22.4±9.9	28.0±10.8	36.9±7.1
Occipital	22.6±3.6	26.8±7.1	37.0±7.3	44.7±8.0
Internal capsule	31.4±5.9	29.9±5.2	29.3±6.7	38.1±9.7†

*Values are mean±SD milliliters per 100 g of brain tissue per minute. PSP indicates progressive supranuclear palsy. Statistical analysis was performed between the groups before and after levodopa administration.

†$P<.05$.

‡$P<.005$.

§$P<.01$.

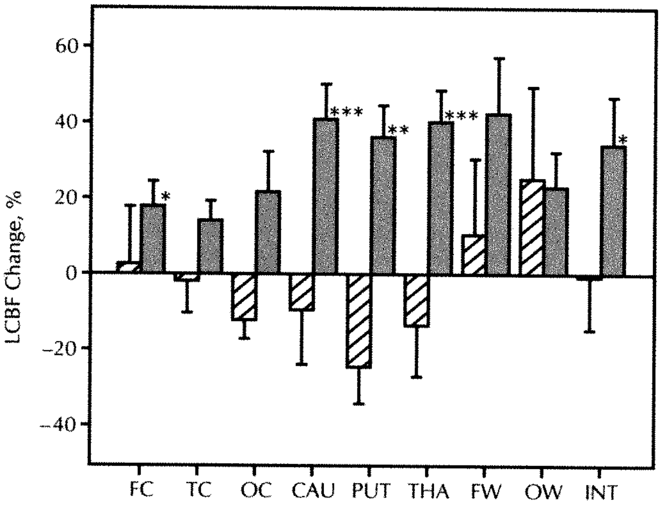

Fig 4.—*Percent changes in local cerebral blood flow (LCBF) after the administration of levodopa in patients with Parkinson's disease (n=9; shaded bars) and in patients with progressive supranuclear palsy (n=5; hatched bars), calculated for nine brain regions. In the patients with Parkinson's disease, the LCBF was increased in most of the brain regions, especially in the basal ganglia, thalamus (THA), and frontal white matter (FW). In the patients with progressive supranuclear palsy, however, the LCBF was unchanged or tended to be reduced (not significantly) following the administration of levodopa. Values are mean±SEM. FC indicates frontal cortex; TC, temporal cortex; OC, occipital cortex; CAU, caudate nucleus; PUT, putamen; OW, occipital white matter; INT, internal capsule; single asterisk,* $P<.05$; *double asterisk,* $P<.01$; *and triple asterisk,* $P<.005$.

Hg). In the patients with Parkinson's disease, LCBF was increased in most of the brain regions after the administration of levodopa. Specifically, the LCBF increments were most prominent and significant in the caudate nucleus ($P<.005$), putamen ($P<.01$), and thalamus ($P<.005$), demonstrating increases of approximately 40%. The LCBF increases were also significant in the frontal cortex ($P<.05$) and internal capsule ($P<.05$). In the patients with PSP, however, there were no increases of LCBF in most of the cerebral regions following the administration of levodopa. Instead, the LCBF tended to decrease in some of the brain regions, although the changes were not statistically significant.

All of the LCBF measurements were completed without any serious side effects, although mild hyperventilation was observed in a few patients.

COMMENT

The problems associated with the xenon-enhanced CT method, such as the anesthetic effects of xenon gas, the effects of the xenon gas itself on the cerebral circulation, motion artifacts, and low signal-to-noise ratio observed with earlier CT scanners, have been discussed previously.[10] This method provides high-resolution, three-dimensional measurements of LCBF in the cerebral cortex as well as in the deep cerebral structures. One of the major problems in studies with single-photon emission CT and positron emission tomography (PET) is that measurements made with extracranial detectors are biased by the presence of brain atrophy. However, the LCBF measurements obtained by the present method are unaffected by this artifact, as the changes in CT numbers during xenon gas inhalation, which form the basis of the LCBF calculation, are not affected by the presence or degree of brain atrophy. The correlation between the LCBF image and brain anatomy is complete.

Baseline LCBF in PSP and Parkinson's Disease

Previous reports have indicated that diffuse or local reductions of CBF were observed in patients with Parkinson's disease.[11-13] Our results on the steady-state LCBF of Parkinson's disease are consistent with those previously reported. In patients with PSP, we found that the LCBF values in most of the brain regions were lower than those in patients with Parkinson's disease. The significant LCBF reduction in the caudate nucleus of patients with PSP is consistent with results obtained by PET, which showed extensive disturbances in the caudate nucleus and putamen.[14] In the cerebral cortex, the LCBF reductions were most prominent in the frontal cortex, at approximately 35% less than those in patients with Parkinson's disease. The so-called hyperfrontality of LCBF (high LCBF values in the frontal cortex) observed in patients with Parkinson's disease was thus lost. Few investigators have studied the LCBF of patients with PSP. Leenders et al,[15] employing PET, found that a diffuse but predominantly frontal reduction of CBF was observed in patients with PSP. Otsuka et al,[16] using PET, demonstrated that the CBF was sharply reduced in the striatum as well as in the frontal cortex in patients with PSP.

Previously reported results for the cerebral metabolism in patients with PSP are not consistent. D'Antona et al[17] and Goffinet et al[18] noted that the glucose metabolism in the frontal cortex was markedly decreased. However, later investigations on the glucose[16,19,20] and oxygen[15,16] metabolism revealed that metabolic depression occurs diffusely in the cerebral cortex as well as in the subcortex, although hypometabolism is relatively strong in the frontal cortex. Our findings concerning the LCBF in patients with PSP are in agreement with these results regarding brain metabolism.

In PSP, pathologic changes in the cerebral cortex per se are known to be rare.[1,17,19] However, dementia is frequently encountered in PSP,[1-3] as it was in all of the patients in our series. Functional disturbances of the cerebral cortex due to primary lesions in the subcortical fibers, especially the afferent fibers to the prefrontal cortex, may account for such dementia.[17] Thus, the dementia observed in PSP has been designated as "subcortical" dementia.[21] It seems likely that the widespread LCBF reductions observed in patients with PSP reflect not only the primary lesions in the subcortex, basal ganglia, and brain stem but also the secondary dysfunction of the cerebral cortex.

LCBF Changes After the Administration of Levodopa in PSP and Parkinson's Disease

In patients with Parkinson's disease, we observed marked LCBF increases in most of the cerebral regions, especially in the corpus striatum and thalamus, following the intravenous injection of 1 mg/kg of levodopa. In contrast, no significant changes were noted in LCBF after the administration of levodopa in patients with PSP. It has been reported by several authors[22,23] that the CBF in Parkinson's disease is not affected by the long-term oral administration of levodopa. Although there are exceptions,[24] the bolus administration of levodopa appears to increase the CBF when given intravenously[25] or orally.[26] Few investigations have examined the regionality of LCBF responses following the administration of levodopa in patients with Parkinson's disease.[13] The detailed effects of levodopa on the LCBF in patients with PSP have not yet been reported.

Two mechanisms might explain the LCBF increases observed after the administration of levodopa in patients with Parkinson's disease: (1) a direct vasodilatory effect of levodopa or its metabolite on the cerebral vasculature and (2) activation of the cerebral metabolism by levodopa or its metabolite, which is followed by alterations in LCBF. Intravenously administered levodopa, which is in itself pharmacologically inert, levodopa is converted into dopamine by the peripheral aromatic L–amino acid decarboxylase.[27] Circulating dopamine may affect the cerebrovascular dimensions via dopamine receptors, which have been found to exist in the cerebral vessels.[28,29] Several in vitro and in vivo investigations have examined the effects of dopamine on the cerebral vessels and CBF.[28-30] However, the results are not uniform, varying according to the animals used, to the methods applied, and to whether the study was performed in vitro or in vivo. Furthermore, regionality of dopamine receptors on the cerebral vessels has not been established. Therefore, the LCBF increases occurring in specific brain regions, such as the striatum and thalamus, following the administration of levodopa could not be explained by its direct vasodilatory effect.

A portion of the intravenously administered levodopa enters the brain through the blood-brain barrier. Levodopa is then converted to dopamine.[27] The dopaminergic system can be activated through the binding of dopamine to dopamine receptors. Because the cerebral metabolism and blood flow are closely coupled,[31] it is possible that levodopa may increase the LCBF through metabolic activation. The corpus striatum, where we observed marked increases in LCBF, is innervated by nigrostriatal dopaminergic neurons.

Thus far, no studies have employed PET to measure directly the alterations in striatal metabolism following the administration of levodopa in patients with Parkinson's disease. In animals, however, it has been demonstrated that the dopamine receptor agonists, apomorphine and piribedil, which may easily penetrate the blood-brain barrier, tend to increase the oxygen metabolism and glucose uptake, and thus secondarily increase the CBF.[32,33] Brooks et al,[14] using PET, showed that while the ^{18}F-6-fluorodopa uptake in the striatum was only partially disturbed in Parkinson's disease, more extensive disturbances were apparent in PSP. The density of dopamine receptors in the striatum is reported to be either unchanged or increased in Parkinson's disease,[34,35] while it is decreased in PSP.[36]

It seems likely, therefore, that the observed differences in LCBF changes following the administration of levodopa between the two diseases reflect differences in the degree of metabolic activation. In Parkinson's disease, in which the dopaminergic neurons and receptors are relatively preserved, they are activated by dopamine, and hence LCBF increases; however, in PSP, in which the dopaminergic neurons and receptors are severely impaired, there is no activation or LCBF increase by dopamine. While the oral administration of levodopa is known to be effective in patients with Parkinson's disease, it is not effective in patients with PSP.[3,4] The differences in LCBF responses to levodopa between the two diseases may be relevant to the differences in the clinical effectiveness of levodopa therapy.

In conclusion, the cerebral hemodynamics observed in PSP and Parkinson's disease reflect the underlying pathologic features of the diseases, such as the degree of preservation of nigrostriatal dopaminergic neurons and the distribution and density of dopamine receptors, and are related to the clinical effectiveness of oral levodopa therapy.

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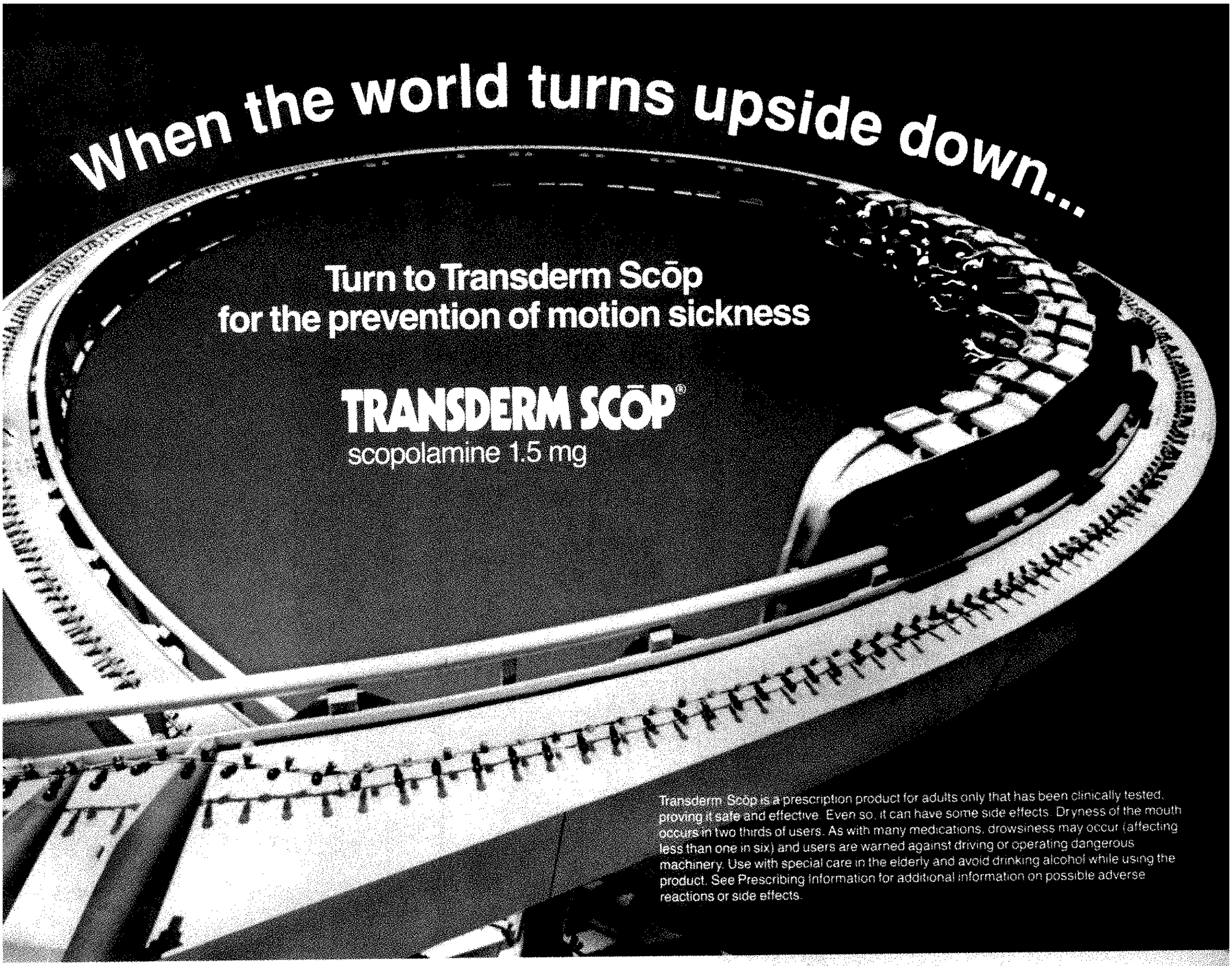
When the world turns upside down...
Turn to Transderm Scōp
for the prevention of motion sickness
TRANSDERM SCŌP®
scopolamine 1.5 mg

Transderm Scōp is a prescription product for adults only that has been clinically tested, proving it safe and effective. Even so, it can have some side effects. Dryness of the mouth occurs in two thirds of users. As with many medications, drowsiness may occur (affecting less than one in six) and users are warned against driving or operating dangerous machinery. Use with special care in the elderly and avoid drinking alcohol while using the product. See Prescribing Information for additional information on possible adverse reactions or side effects.

Transderm Scōp®

scopolamine
(formerly Transderm-V)

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

Transdermal Therapeutic System

Programmed delivery *in vivo* of 0.5 mg of scopolamine over 3 days

INDICATIONS AND USAGE

Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS

Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS

Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

***Handling:** After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear. The system should be stored between 59°-86°F (15°-30°C).

CAUTION

Federal law prohibits dispensing without prescription.

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Division of CIBA–GEIGY Corporation
Summit, NJ 07901

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"As doctors, if we do the right thing at the right time, we can make a difference."

Dr. Kenneth A. Haller, Pediatrician, East St. Louis, Illinois, Member, American Medical Association

In one of the nation's poorest communities, Dr. Kenneth Haller is working not only to save children's lives, but to bring dignity to the lives of their parents.

He is the type of physician who brings distinction to our profession. He is the type of physician who upholds the highest ideals of medicine. He is also a member of the American Medical Association (AMA).

"I read the Principles of Medical Ethics of the AMA and was impressed by it. I'm proud to be a member," says Dr. Haller.

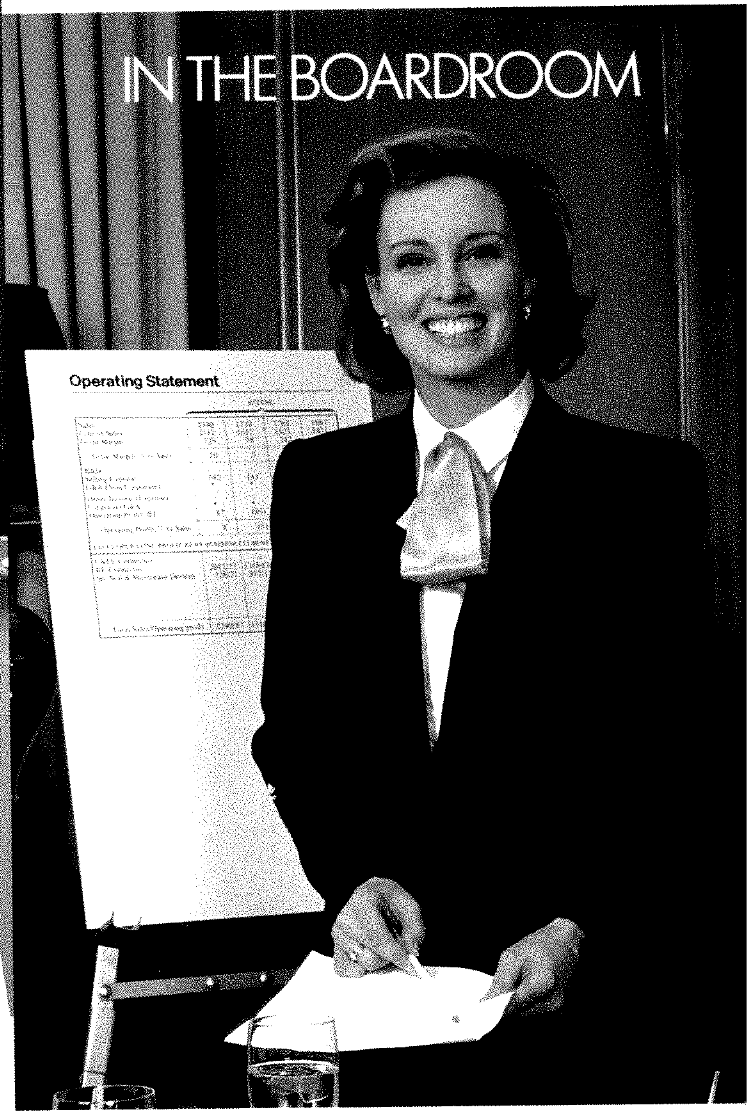
You are invited to join Dr. Haller and to join with him in his efforts to bring quality health care to those in need. To become a member of the AMA, call our toll-free number now. 1-800-AMA-3211.

American Medical Association

Physicians dedicated to the health of America

Seizures controlled, thoughts clear, smiles bright

IN THE CLASSROOM...



Low risk of cognitive impairment[1]

Generally avoids hirsutism[2,3]

Avoids gingival hyperplasia[2,3]

BASEL

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Tegretol®

200-mg scored tablets
100 mg chewable tablets

carbamazepine USP

...because after seizure control, there's a lot of living to do!

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the next page, especially the boxed warning.

References:

1. Smith DB, Mattson RH, Cramer JA et al. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia*. 1987;28(suppl 3):S50-S58.

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Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg—red-speckled, pink
Tablets of 200 mg—pink
Suspension of 100 mg/5 ml

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

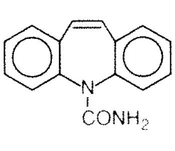
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, and as a suspension of 100 mg/5 ml (teaspoon). Its chemical name is 5*H*-dibenz[b,f]azepine-5-carboxamide, and its structural formula is:



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Tablets: Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

In clinical studies both suspension and conventional tablet delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster than the tablet. Following a b.i.d. dosage regimen, the suspension has higher peak levels and lower trough levels than those obtained from the tablet formulation for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4 to 5 hours after administration of oral tablets. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

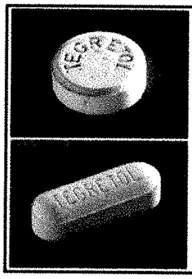
1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.



Only TEGRETOL
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10,11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid, fluoxetine or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of

6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: Either 200 mg b.i.d. for tablets or 1 teaspoon q.i.d. for suspension (400 mg per day). Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: Either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension (200 mg per day). Increase at weekly intervals by adding up to 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg/daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100 . . . . NDC 58887-052-30
Unit Dose (blister pack)
  Box of 100
  (strips of 10) . . . . NDC 58887-052-32

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

  Bottles of 100 . . . . NDC 58887-027-30
  Bottles of 1000 . . . . NDC 58887-027-40
Unit Dose (blister pack)
  Box of 100
  (strips of 10) . . . . NDC 58887-027-32

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture. Dispense in tight container (USP).

Suspension 100 mg/5 ml (teaspoon)—yellow-orange, citrus-vanilla flavored

  Bottles of 450 ml . . . . NDC 58887-019-76

Shake well before using.
Do not store above 86°F.
Dispense in tight, light-resistant container (USP).

Printed in U.S.A. C91-50 (Rev. 11/91)

BASEL Pharmaceuticals

BASEL Pharmaceuticals
Division of
CIBA-GEIGY Corporation
Summit, New Jersey 07901

Dosage Information: Tablets and Suspension

Indication	Initial Dose		Subsequent Dose		Maximum Dose
	Tablet	Suspension	Tablet	Suspension	Tablet or Suspension
Epilepsy 6-12 years of age	100 mg b.i.d. (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 100 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 1 teaspoon (100 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours
Over 12 years of age	200 mg b.i.d. (400 mg/day)	1 teaspoon q.i.d. (400 mg/day)	Add up to 200 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 2 teaspoons (200 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours: 12-15 years 1200 mg/24 hours: over 15 years 1600 mg/24 hours: adults, in rare instances
Trigeminal Neuralgia	100 mg b.i.d. on the first day (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 200 mg per day in increments of 100 mg every 12 hours	Add up to 2 teaspoons (200 mg) per day q.i.d.	1200 mg/24 hours

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Original Contribution

Cerebral Brain Metabolism in Adult Dyslexic Subjects Assessed With Positron Emission Tomography During Performance of an Auditory Task

Jennifer O. Hagman, MD; Frank Wood, PhD; Monte S. Buchsbaum, MD; Paula Tallal, PhD; Lynn Flowers, PhD; William Katz, PhD

• Ten dyslexic adults (aged 33.5±7.3 years, nine men, one woman) and 10 age-, sex- and handedness-matched control subjects (aged 33.6±5.8 years) performed an auditory syllable discrimination task during 18-fluoro-2-deoxyglucose uptake, and then underwent positron emission tomographic scans. A second normal control group performed an analogous visual discrimination task. Dyslexic subjects experienced greater difficulty and made significantly more errors in performing the auditory task. There were no differences in brain metabolic rates in lateral cortical areas (frontal, parietal, temporal, and occipital lobes). A significant difference emerged in the medial temporal lobe, with dyslexic subjects having significantly higher absolute and relative brain metabolism along an anterior-posterior gradient than normal adults. These data support the hypothesis of altered cerebral processing of auditory stimuli in patients with dyslexia.

(*Arch Neurol.* 1992;49:734-739)

Dyslexia is a problem in which the affected individual experiences academic difficulties that are the result of perceptual processing deficits. Most professionals in the field agree that learning is neurologically based, and that dyslexia is a form of learning disability related to reading, the recognition of words, and the interpretation of what is seen visually or heard auditorily that is the result of a neurophysiologic dysfunction.[1]

However, studies confirming perceptual deficits have not determined a structural/functional basis for dyslexia. Previous studies of dyslexia using event-related potentials,[2] magnetic resonance imaging, and computed tomography [3,4] have yielded interesting, but nonspecific findings. Flowers et al[5] performed a series of studies using regional cerebral blood flow and event-related potentials to investigate a hypothesized left temporal lobe substrate for developmental dyslexia. The authors concluded that brain function in subjects with dyslexia differs from that in normal control subjects when dyslexic subjects perform tasks requiring phonemic discrimination or orthographic analysis, and that the left temporal lobe may be the site of this difference. A regional cerebral blood flow study by Wood et al[6] reported that childhood reading ability was inversely correlated with focal activation in the posterior, temporoparietal area of the cortex, whereas normal subjects activated a left superior temporal focus while performing the same orthographic task. They interpreted their results as suggestive of a trait anomaly of left hemisphere cerebral activation in adults who were dyslexic as children. Two other regional cerebral blood flow studies[7,8] did not find left hemisphere verbal processing deficits in dyslexic males. However, these studies were not well controlled, and the activation tasks used during the procedure were not closely related to language mechanisms involved in reading disability. Positron-emission tomographic (PET) scanning provides a unique opportunity to study brain activity while the individual performs a task.

Tallal[9] hypothesized that "because acquisition of phonics skills is dependent on intact auditory and phonetic processing abilities, children who develop reading impairments might suffer from a similar deficit in processing rapidly changing acoustic stimuli, as seen in children with language impairments." Tallal and Piercy[10] subsequently developed the repetition test, which tests the primary components of temporal processing: temporal resolution, discrimination, sequencing, and rate perception. Using the repetition test, they confirmed that language-impaired children have difficulty processing speech sounds that are characterized by rapidly changing acoustic spectra that are critical for speech discrimination,[11-13] specifically consonant-vowel syllables. Based on these findings, we developed an auditory version of the continuous performance task (CPT), which tests stop consonant-vowel syllable discrimination.

Using PET we can look for patterns of brain activity specific to the dyslexic subject, compared with normal in-

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dividuals. This will be best accomplished by the selection of a task that activates regions of the brain that may be involved in dyslexia. The goal of our study is to develop a clinically useful profile of brain activity, with potential diagnostic and treatment implications for children and adults with dyslexia.

SUBJECTS AND METHODS

Subjects

Ten adult subjects (aged 33.5±7.3 years) who had been originally studied as children and diagnosed as having profound reading disabilities were located, retested, and extensively studied by one of us (F.W. and colleagues). The dyslexic subjects had been referred to the Orton Reading Center in Winston-Salem, NC, during its operation between 1957 and 1972. Their childhood records, accessed with written permission, are maintained at the Health Sciences Library of Columbia University, New York, NY. Criteria for inclusion in the dyslexic group included normal IQ, no significant psychiatric or other neurologic disorder, and no history of attention deficit disorder (Table 1). To participate in our study, dyslexic subjects had to be at least 2 SDs below normal in their reading abilities as calculated using the regression equation developed by Finucci et al.[14] Dyslexia was defined by Gray Oral Reading Test[15] and Wide Range Achievement Test[16] scores that were 1.5 years behind grade level during childhood, and a Finucci Average Deviation Score that was 2 SDs below the mean (Table 1). There were nine men and one woman in the dyslexic group, and one of the men was left-handed. Control subjects for the auditory CPT were obtained from the University of California, San Diego, and were matched one to one per each dyslexic subject on the basis of age, IQ, sex, and handedness. The 10 age- (33.6±5.8 years), sex-, and handedness-matched control subjects performed the same auditory task. The auditory control subjects also were tested with the Gray Oral Reading Test,[15] the Wide Range Achievement Test,[16] and the Finucci Average Deviation Score,[17] and all were within normal limits. There were no significant differences between dyslexic and auditory control subjects in age, sex, or performance IQ (Table 1). The dyslexic subjects had a significantly lower verbal IQ (Table 1), although their mean score was still within the normal range. In addition, 10 age- (33.2±4.8 years), sex-, and handedness-matched normal, nondyslexic subjects served as a control group for the visual task condition (Table 1).

Task

Dyslexic subjects and auditory control subjects performed an auditory version of the CPT. Flowers et al[5] have reported correlations between these same subjects' auditory CPT performance, and brain metabolism. The auditory CPT is a speech discrimination activation task. Six stop consonant-vowel syllables (a, da, ga, pa, ta) were computer digitized. Each speech stimulus was 250 milliseconds long, and incorporated a transitional component in the initial segment of the speech stimulus of 40 milliseconds. Stimuli were presented every 2 seconds, and subjects were trained to press a response button whenever the target syllable da was presented. The target syllable was presented randomly among the other stimuli with a probability of occurrence of about 25%. Speech stimuli were degraded with "cocktail party speech" background noise to the extent that normal subjects responded at 75% correct to the target syllable. During the PET procedure, these speech stimuli were presented randomly for 30 minutes after the ^{18}F-fluorodeoxy-2-glucose glucose tracer was administered. The visual task control group performed the CPT (CPT [17,18]) during ^{18}F-fluorodeoxy-2-glucose uptake. Performance for both tasks was assessed with the signal detection measure d'; perfect discrimination is 4.1, and chance discrimination, 0.0.[19,20]

PET Procedure

Subjects performed the task in a darkened, soundproof room during ^{18}F-fluorodeoxy-2-glucose uptake. Immediately after the 30-minute period of uptake, they were transferred to the PET scanner (NeuroEcat) for the PET scan, which lasted approximately 45 to 80 minutes. A custom-formed thermoplastic mask holds the subject's head still and in position in the scanner. The resolution of the scanner is 7.6 mm in plane and 9.9 mm axially. Data were converted into metabolic rate as described elsewhere.[21]

Table 1.—Clinical Characteristics of Subjects*

	Mean±SD		
	Dyslexic Subjects	Auditory	Visual CPT
Age, y	33.±7.3	34.±5.8	33.±4.8
Education/	15.6±2.7	14.9±2.3	. . .
Gray Oral Reading Test	42.7±11.1	93.8±8.7†	. . .
WRAT	17.±4.9	33.±5.9†	. . .
Verbal IQ	96.±10.5	106.±10.6‡	. . .
Performance IQ	103.±8.1	106.±9.8	. . .
Finucci	−2.8±0.9	1.8±1.3†	. . .

*CPT indicates continuous performance task; WRAT, Wide Range Achievement Test.

†$P<.00001$.

‡$P=.052$.

Statistical Analysis

For analysis of cortical data, the outer brain contour of each slice was outlined with a boundary-finding technique developed for skull computed tomographic scans as described by Buchsbaum et al.[22,23] For subcortical and medial frontal regions, images from the Matsui and Hirano[24] atlas were photographed, digitized, and stored for reference, and coordinates of identified regions adjusted for slice length and width were applied to the PET slices.[21] Analyses were carried out both on absolute values of glucose in micromoles per 100 g of tissue per minute and on relative glucose expressed as regions of interest divided by the mean glucose metabolic rate in a whole slice.

Glucose data were analyzed using repeated measures of analysis of variance (BMDP [25]). This approach was chosen because the multiple determinations of metabolic rate within each subject were arranged in discrete dimensions. Two separate analyses were performed: (1) the two normal control groups, auditory vs visual task; (2) dyslexic subjects vs normal subjects performing the auditory task. Since the main effects of the brain lobe were always significant, only the significant interactions that contain group are presented.

RESULTS

Dyslexic subjects identified syllables more poorly than normal control subjects did (mean=2.62, SD=.52 vs mean=3.54, SD=.52, $t=4.00$, $df=18$, $P=<.01$).

To confirm that the auditory task activates the temporal lobe, we compared PET scans of normal adults performing the visual CPT during ^{18}F-fluorodeoxy-2-glucose uptake to the auditory control group. This was done with a four-way analysis of variance with task (visual, auditory) as an independent group dimension and lobe (frontal, parietal, temporal, occipital), gyrus (four regions within each lobe, Fig 1), and hemisphere (left, right). Relative temporal lobe metabolism was higher and frontal/parietal metabolism lower in the auditory CPT task group than in the visual CPT group (Table 2). Occipital metabolism was unchanged. These regional differences were statistically confirmed with a significant relative metabolic rate lobe by group interaction; no other interactions with group were significant. The absolute metabolic rates for lateral cortical

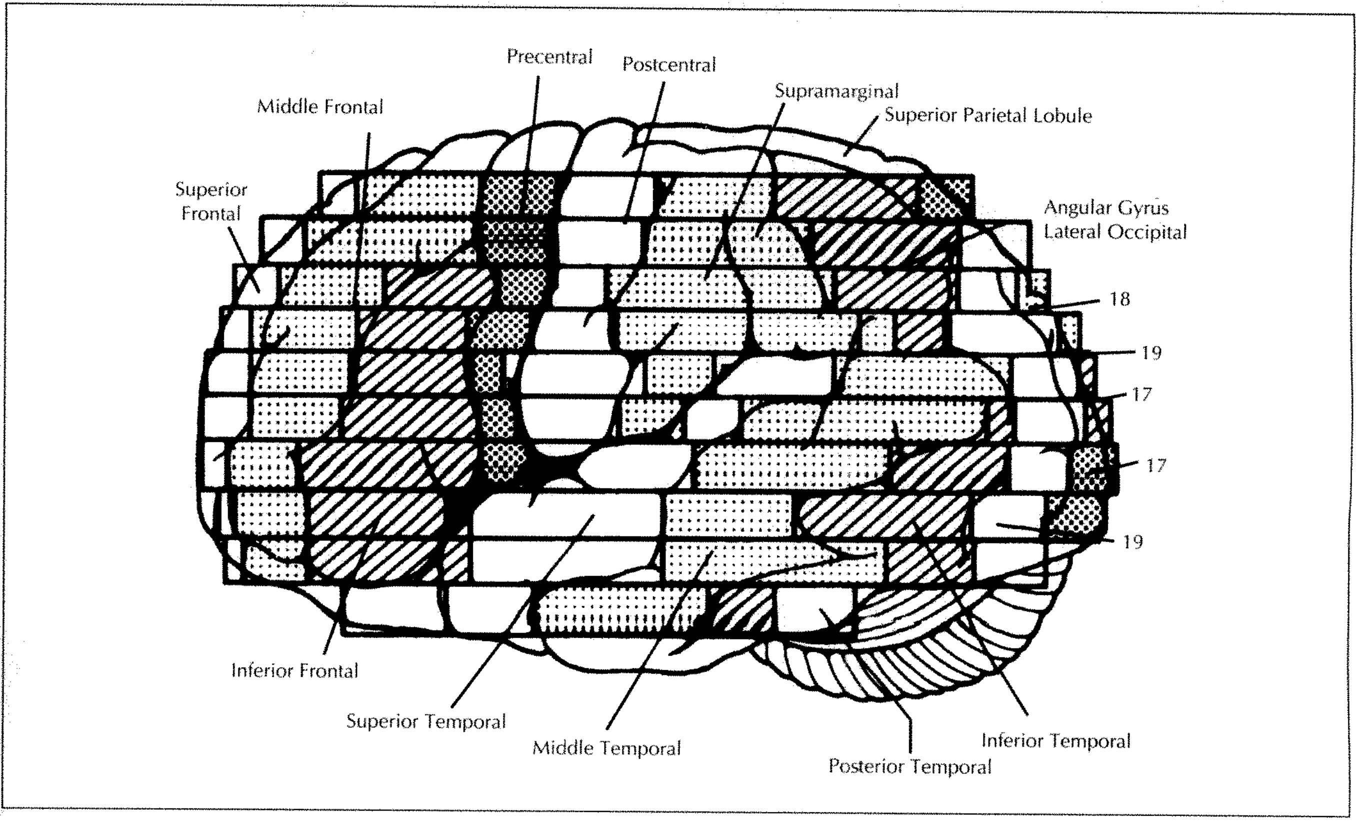


Fig 1.—*Lateral cortical surface showing 16 regions of interest. Metabolic rate was calculated for each area across slices and each slice contribution weighted in proportion to its contribution to the surface of each named area. Area 19 was divided into a dorsal and ventral half.*

areas showed a similar pattern, which approached, but did not achieve significance. Follow-up *t* tests on the relative data showed the superior, middle, and inferior temporal lobe to be higher in auditory than visual CPT on both sides. No significant differences were found in either relative or absolute metabolism for the dyslexic vs auditory control groups.

Both the auditory and visual tasks showed greater left- than right-sided activity in the motor and sensory strips, consistent with the use of the right hand. This reached significance for the sensory strip for the auditory task (mean=17.1, SD=4.5 vs mean=15.9, SD=4.5, paired t=3.9, P<.01) and was of borderline significance for the motor strip (18.1, SD=4.9 vs 17.6, SD=4.8, paired t=1.69, P=.11, two tailed). Similar results were seen for relative data.

We next performed an analysis of a combination of cortical and subcortical structures chosen to sample frontal, limbic, and striatal systems (Tables 3 and 4). There was a significant difference between the visual and auditory tasks, for both relative and absolute metabolism, with auditory activation of the left hemisphere and visual activation of the right. We found a bilateral decrease in metabolism in medial structures (including cingulate) and a right hemisphere decrease in the basal ganglia and thalamus for the auditory task group (Tables 3 and 4). There were no significant differences in metabolism in the same areas between the dyslexic group and the auditory control group, although the increased metabolism in medial white structures and the reversed hemisphere effect in nuclei are of note (Tables 3 and 4).

To analyze medial temporal lobe structures, a special template was created (Fig 2). These areas were first analyzed by grouping the anterior-most regions from each section, followed by medial regions and posterior regions. The brain metabolism rates for these regions were entered into a four-way analysis of variance with diagnostic group (dyslexia, normal), hemisphere (left, right), and slice level (Matsui and Hirano[24] atlas slice levels 9, 10, 11). A significant difference emerged between dyslexic subjects and auditory control subjects in both the absolute and relative analysis. Dyslexic subjects were found to have significantly higher metabolism in medial temporal lobe structures in an anterior to posterior gradient (Tables 5 and 6 and Fig 3). A second analysis of medial temporal lobe structures looked at the seven regions within each of the three slices. There was no hemisphere effect for relative or absolute metabolism between dyslexic and control subjects. A significant area by region by group interaction (Table 7) was found for relative metabolism. There were no significant differences in relative or absolute metabolism between the visual CPT task group and the auditory control task group in medial temporal regions.

Table 2.—Lateral Cortical Areas (Relative Metabolic Rates)*

Lobe	Task Group, Mean±SD	
	Visual	Auditory
Frontal	1.15±.09	1.12±.09
Parietal	1.16±.12	1.12±.11
Temporal	0.89±.12	0.97±.13
Occipital	1.13±.13	1.14±.14

*Analysis of variance: lobe by group effect, P=.05, F=3.07, df=2.16, 38.91.

Table 3.—Cortical and Subcortical Structures (Relative Metabolic Rates)*

	Task Group, Mean±SD					
	Visual		Auditory		Dyslexic	
Region	Left	Right	Left	Right	Left	Right
Cortex	1.07±.13	1.09±.13	1.08±.10	1.09±.09	1.08±.11	1.09±.10
Medial	1.11±.11†	1.10±.11‡	1.04±.15	1.03±.14§	1.12±.16	1.08±.17
Nuclei	1.22±.14	1.30±.14	1.24±.19	1.20±.19	1.20±.22	1.24±.19
Mean	1.13±.14	1.16±.16	1.12±.17	1.11±.16	1.13±.17	1.14±.17

*Cortex: frontal lobe, parietal lobe, temporal lobe, occipital lobe; medial: medial frontal lobe, anterior, medial, and posterior cingulate; and nuclei: caudate, putamen, globus pallidus, and thalamus. Analysis of variance: task effect, visual vs auditory continuous performance task; hemisphere by group, $P=.0386$, F=4.56, *df*=1.63, 29.32. Region by hemisphere by group, $P=.0249$, F=4.98, *df*=1, 18. Analysis of variance: auditory vs dyslexia, not significant.

†*T* test: visual vs auditory task, $P=.04$.

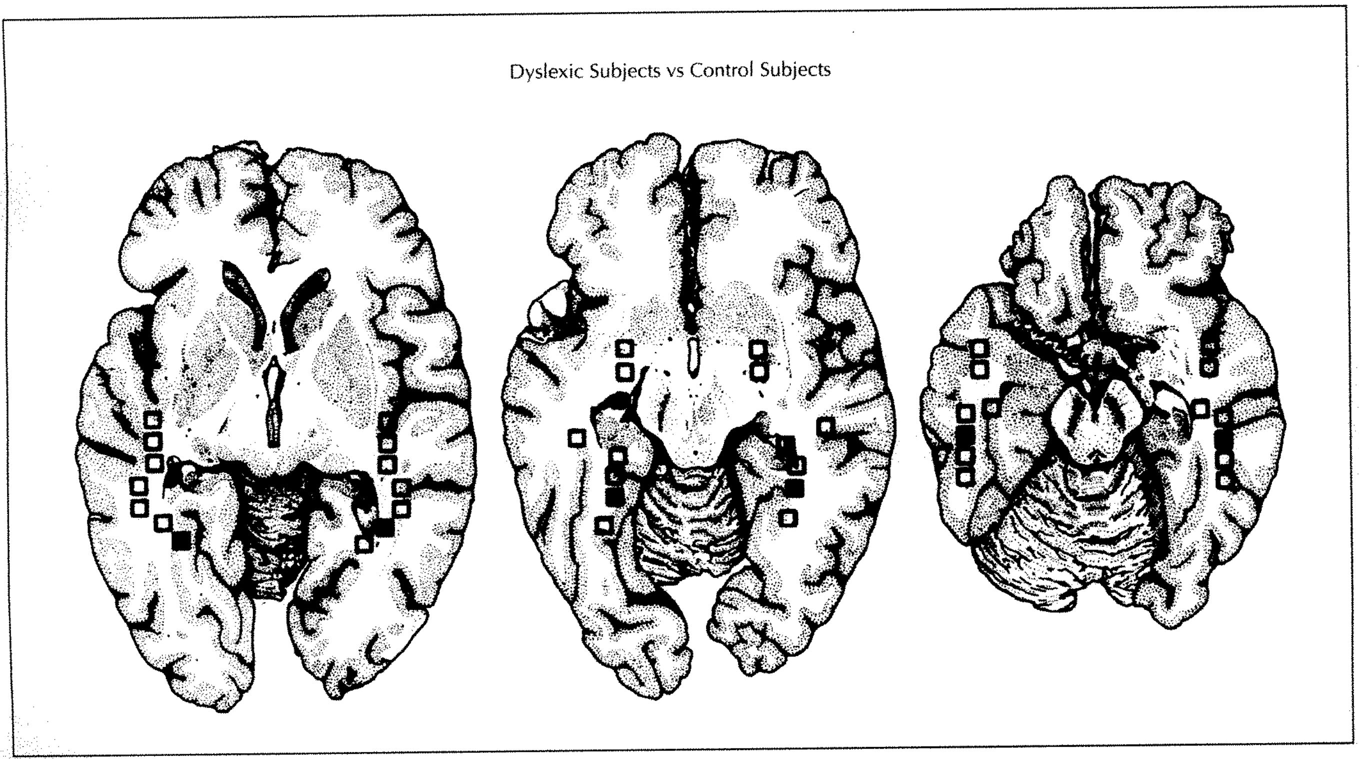
‡*T* test: visual vs auditory task, $P=.10$.

§*T* test: auditory vs dyslexic, $P=.02$.

Table 4.—Cortical and Subcortical Structures (Absolute)*

	Task Group, Mean±SD					
	Visual		Auditory		Dyslexic	
Region	Left	Right	Left	Right	Left	Right
Cortex	16.9±4.9	17.2±5.0	15.8±4.0	16.0±4.0	16.7±2.8	16.9±3.0
Medial	18.1±5.3	17.8±4.6	15.8±5.0	15.8±5.0	18.1±4.2	17.4±4.3
Nuclei	19.1±4.4	20.7±6.0	18.5±4.8	17.9±4.5	18.9±4.9	19.5±4.2
Tot-Hem	18.0±4.5	18.5±5.4	16.7±4.7	16.6±4.6	17.9±4.1	17.9±4.0

*Analysis of variance task effect, visual vs auditory continuous performance task, region by hemisphere by group, $P=.03$, F=4.46, *df*=1.45, 26.02. Hemisphere by group, $P=.045$, F=4.62, *df*=1, 18. Analysis of variance: auditory vs dyslexia not significant.



Dyslexic Subjects vs Control Subjects

Fig 2.—*The temporal lobe template contains three sections of the brain (anterior to posterior) that contain medial temporal lobe structures. Seven regions were identified on each of the three sections. The darkened boxes represent regions where dyslexic subjects were significantly different from control subjects (P<.05).*

Table 5.—Temporal Lobe Metabolic Rate*

Slice	Temporal Lobe, Mean±SD	
	Control	Dyslexic
Anterior		
1	19.6±2.0	19.7±1.4
2	18.5±2.0	18.7±1.2
3	11.9±1.5	15.3±1.7
Middle		
1	16.3±1.6	15.6±1.1
2	14.9±1.2	15.9±0.9
3	14.5±1.1	15.3±0.6
Posterior		
1	16.4±1.8	18.8±1.5
2	16.1±1.3	18.4±1.4
3	15.3±1.3	15.1±0.8

*Analysis of variance, anteroposterior by slice level by group interaction, *P*=.0548, F=2.64, *df*=3.19, 57.48.

Table 6.—Temporal Lobe Relative Analysis*

Slice	Mean±SD	
	Control	Dyslexic
Anterior		
1	0.99±.29	0.97±.30
2	1.03±.39	1.01±.33
3	0.77±.44	0.92±.40
Middle		
1	0.82±.24	0.77±.30
2	0.84±.15	0.85±.16
3	0.96±.17	0.94±.21
Posterior		
1	0.84±.45	0.93±.36
2	0.93±.46	0.99±.33
3	1.01±.27	0.93±.21

*Analysis of variance, anteroposterior by slice level by group, *P*=.0258, *df*=3.47, 62.46, F=3.13.

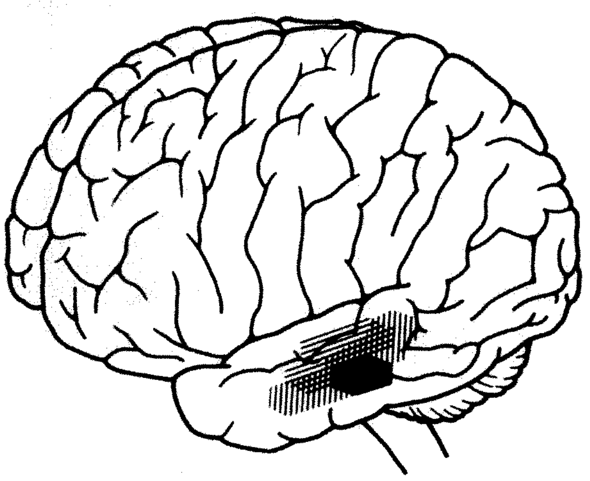


Fig 3.—*Higher brain metabolism was found in medial temporal lobe structures of dyslexic subjects, in an anterior-to-posterior gradient.*

Table 7.—Temporal Lobe, Subcortical Template, Relative

Slice	Mean±SD		
	Auditory	Dyslexic	
Anterior (1)			
1	1.04±.15	1.04±.14	
2	0.92±.17	0.89±.21	
3	0.78±.15	0.77±.25	
4	0.81±.17	0.75±.20	
5	0.82±.15	0.79±.15	
6	0.81±.25	0.87±.19*	*P*=.04
7	0.87±.23	0.97±.22	
Middle (2)			
1	1.05±.20	1.04±.16	
2	1.00±.21	0.98±.20	
4	0.79±.15	0.81±.17	
5	0.88±.14	0.88±.11	
6	0.88±.17	0.91±.16	
7	0.91±.23	0.97±.19*	*P*=.045
8	0.94±.25	0.9±.18	
Posterior (3)			
1	0.62±.32	0.87±.32	
2	0.92±.19	0.97±.20	
4	0.84±.13	0.82±.14	
5	1.06±.17	1.04±.17	
6	1.06±.16	1.00±.20*	*P*=.03
7	1.01±.15	0.93±.16	
8	1.01±.15	0.92±.12	

*Analysis of variance AR×G, *P*=.05, F=2.08, *df*=6.70, 120.62.

COMMENT

These results suggest that brain metabolism in dyslexic adults differs from that in normal adults performing the same auditory discrimination task. Although there were no differences in lateral cortical metabolism (including temporal lobe), dyslexic subjects had higher metabolic rates in medial temporal regions. The boxes are adjacent to the gray matter of the hippocampus and middle temporal gyrus, and assess both medial gray and white matter of the temporal lobe.

The temporal lobe receives auditory information, and it controls memory and language. Although the perception of language is believed to be a left hemisphere function, our subjects did not activate the left hemisphere predominantly; instead, there was bilateral activation during this task. The area of increased metabolism found in the dyslexic group in medial temporal lobe structures corresponds to the area just below the medial occipitotemporal gyrus (Fig 3). Afferent fibers connecting the medial geniculate body to area 41 of the superior temporal lobe, a primary auditory processing center, are found in the white matter below the medial occipitotemporal gyrus.

Wernicke's area of the lateral temporal lobe permits us to recognize information presented in auditory form. This lateral part of the temporal lobe also was not significantly different between groups. It is possible that the brains of dyslexic adults have developed compensatory pathways for processing auditory information. In our study, dyslexic subjects showed a pattern of increased metabolism in medial temporal lobe structures that contain afferent fibers believed to relay auditory stimuli to primary auditory processing centers. This may be the result of inefficient processing, or activation of compensatory pathways during performance of an auditory perception task that is difficult for dyslexic subjects. These data support the hypothesis of altered cerebral processing of auditory stimuli by the temporal lobe in subjects with dyslexia, but fail to support a left temporal lobe predominance in dyslexic pathology.

The regions of interest in the medial temporal lobe fall both in areas that are primarily gray and primarily white. The post-hoc tests suggest that the greatest statistical power comes from medial gray areas. Since dyslexic subjects showed increased rates, changes in metabolic rate from artifacts of cortical shrinkage and partial volume effects seem unlikely to be explanatory. However, decreases in white matter volume relative to gray in dyslexic subjects or increases in white matter metabolic rate cannot be excluded.

Further research is necessary to clarify the nature and significance of alterations brain metabolism in dyslexia. As part of this study, we will be analyzing electroencephalographic and magnetic resonance imaging data from the same subjects, and correlating the findings with the PET data. Future PET studies of dyslexia should attempt to include children as well as adults, and should incorporate visual tasks in addition to auditory tasks to elucidate additional insight into how the brain learns and processes different stimuli, and how these capacities can be altered in the dyslexic brain.

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Peripheral Mechanical Loading and the Mechanism of the Tremor of Chronic Alcoholism

Mindy L. Aisen, MD; B. Dov Adelstein, PhD; Jorge Romero, MD; Alethea Morris; Michael Rosen, PhD

• The tremor of chronic alcoholism, although clinically similar to essential tremor, has been considered a distinct syndrome. Its underlying mechanism was analyzed in five patients (none in the acute stages of alcohol withdrawal) hospitalized in an alcohol detoxification program. All five patients performed tracking tasks in which they pursued a linearly moving "target" light with a response light that they controlled by flexion-extension activity of the wrist. Stationary and dynamic targets were used with both isometric and unconstrained wrist mechanical interfaces. Frequency, torque, and displacement tremor characteristics were examined under varying inertial loading or isometric voluntary torque conditions. Two simultaneous tremor components were present in all patients: a prominent 4- to 7-Hz low-frequency peak and a smaller-amplitude 9.4- to 9.6-Hz high-frequency peak. As the inertia of the hand was augmented during unconstrained tasks, the low-frequency peak decreased, while the high-frequency peak was unaffected. As required voluntary effort was increased during isometric testing, the amplitude of the low-frequency peak increased. These findings suggest that the low-frequency peak represents the significant pathologic component of the tremor of chronic alcoholism and that it has a biomechanical reflex mechanism similar to that of the lower-amplitude normal physiologic tremor.

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The tremor of chronic alcoholism has a frequency content that is similar to that of essential tremor,[1-3] although clinical differences have been described that suggest that it is a distinct syndrome.[4] To examine its underlying mechanism, we analyzed changes in its frequency components under varying external mechanical conditions in five patients with chronic alcoholism following detoxification.

PATIENTS AND METHODS

Five consecutive patients with chronic alcoholism hospitalized in the alcohol detoxification service of the Veterans Affairs Medical Center, Brockton, Mass, were selected for study after being alcohol free for more than 30 days. Clinical assessment was independently performed by two neurologists, who graded tremor amplitude as absent, minimal, mild to moderate, moderate, and severe and during rest, postural maintenance, and action.

All patients had a visually obvious rapid tremor of mild to moderate amplitude. The severity of postural and kinetic components varied among subjects. In all patients, tremor had developed after an extended period of alcohol abuse. Four of the five patients had no family history of tremor. One patient (No. 4) reported that his father's "hands shook" but was unable to describe the tremor history or characteristics in any detail. A summary of patient clinical characteristics is shown in the Table. In addition to the drugs listed, patient 1 had also been treated with propranolol hydrochloride, which did not suppress the tremor.

Tremor frequencies and displacement amplitude were examined under varying inertial loading, while frequencies and torque amplitude were measured under isometric voluntary torque conditions. All five patients performed a visually presented pursuit tracking task. A linearly moving "target" light on a light-emitting diode bar graph display was pursued by a response light controlled by flexion-extension activity of the subject's wrist; the response cursor was governed by either a flexion-extension angle tranducer or an isometric torque transducer, depending on the type of tracking task being performed. A matrix of four tracking tasks was presented. Two target types (stationary and dynamic) were coupled with two mechanical interfaces (free-moving and isometric). All tracking tasks were conducted in a horizontal plane, ie, with the wrist flexion-extension axis parallel to gravity.

During unconstrained dynamic testing, tracking tasks that required ±30° of flexion-extension movement at the wrist were conducted while varying inertial loads (0 to 1.5 kg) were applied to the palmar aspect of the device handle. The device handle was constructed of 1.3-cm-gauge aluminum, and the estmated equivalent inertia of the hand about the wrist ranged from 0.0054 kg-m^2 for the unloaded handle to 0.028 kg-m^2 with the largest mass.[5] During isometric dynamic testing, varying amounts of voluntary force were applied by the subject to the device handle, which was locked about the wrist axis. Isometric wrist flexion-extension torque was transduced to drive the response light, and the "load" was varied by changing the gain from the wrist torque transducer to the display. Reduced gain required greater torque to follow the same target excursions. Peak voluntary flexion-extension torques ranged from 0.45 to 2.25 N-m.

Static tasks, in which subjects maintained a constant wrist angle, were included to assess tremor during postural maintenance activities. Because of the horizontal orientation chosen for the experiments, a constant force spring was used to pull on the palmar as-

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Summary of Patient Clinical Characteristics*

Patient No./ Age, y	Duration of Alcoholism, y	Duration of Tremor	Family History	Amplitude			Suppressed by	
				Rest	Postural	Kinetic	Alcohol	Diazepam
1/46	30	1 y	No	+	++++	+++	Yes	No
2/53	10	2 mo	No	+	+++	+++	No	Yes
3/62	10	1 y	No	+	+++	+++	CNE	CNE
4/28	16	13 y	Yes	+	++	+++	Yes	CNE
5/41	20	20 y	No	+	+++	+++	Yes	CNE

*Single plus sign indicates mild; double plus, mild to moderate; triple plus, moderate; quadruple plus, severe; and CNE, cannot evaluate.

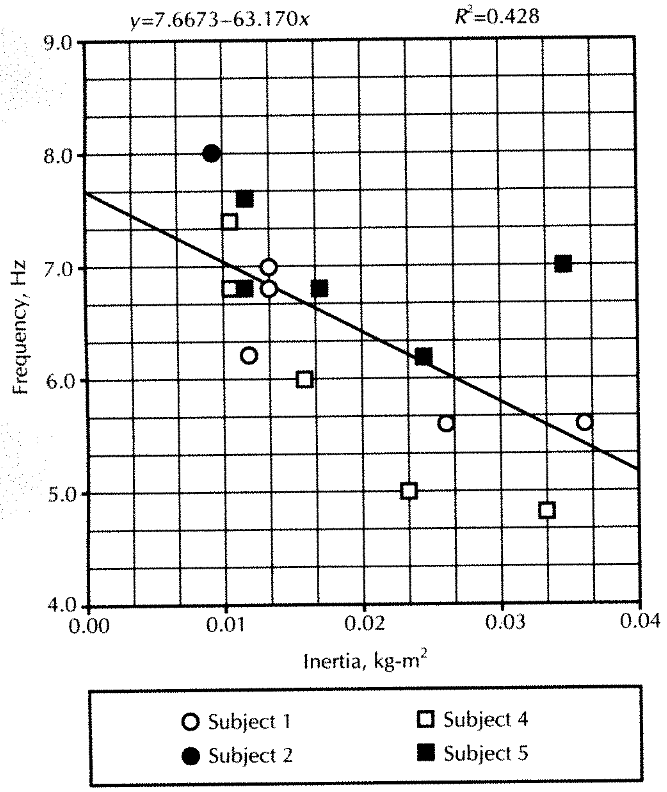

Fig 1.—*Unconstrained position maintenance: low-frequency tremor.*

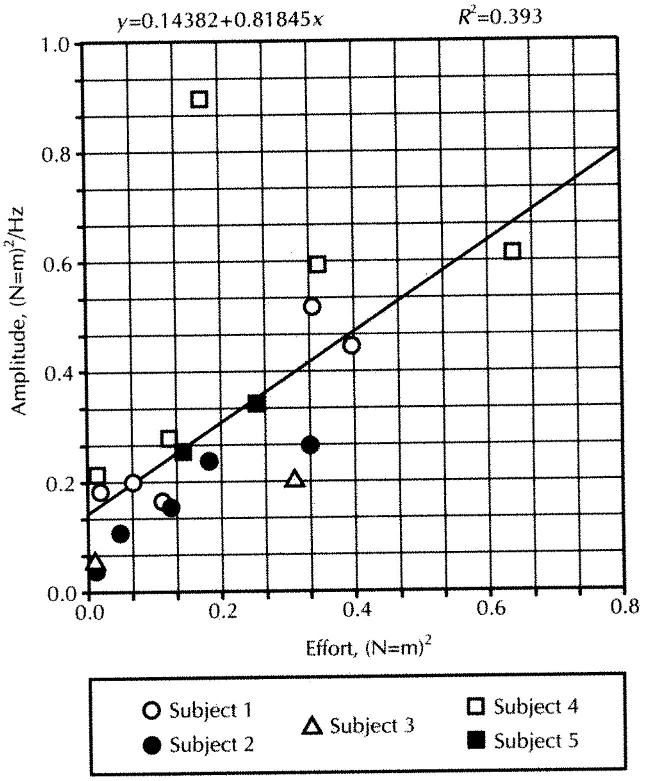

Fig 2.—*Isometric dynamic tracking: low-frequency tremor.*

pect of the hand to simulate gravitational forces in the free-moving types. Static isometric trials were conducted at the same gain settings as in dynamic tests. A complete description of the apparatus employed in the protocol has been previously published.[5,6]

DATA ANALYSIS

The data were subjected to frequency domain analysis to obtain measures of purposeful tracking and involuntary tremor. Tremor was defined as the activity contained in the "noise" portion of the response, ie, the components not linearly related to the target.[1] Tremor frequencies and associated peak power densities were read directly from the spectral plot of the nonlinear response data. Significant variation of tremor characteristics with the experimental variables was detected by linear regression. Data from all tested subjects were pooled for the purpose of this analysis.

RESULTS

In all patients, the tremor spectra showed two simultaneous peaks, one with a relatively large amplitude and a lower frequency (LF) (5.2 to 7.6 Hz) and one with a smaller amplitude and a higher frequency (HF) (9.4 to 9.6 Hz). The behavior of these peaks were examined as experimental conditions changed. Two effects were observed.

During unconstrained testing, the LF tremor peak diminished in frequency as the hand inertia was augmented ($P<.005$). The frequency of the faster tremor peak was unaffected. Figure 1 demonstrates the relationship between LF and inertia during unconstrained postural maintenance. The data for patient 3 were not available for this trial because of recording failure. However, this patient had the same inverse relationship between frequency and inertia during dynamic testing.

During isometric testing, the LF peak increased in amplitude as greater voluntary effort was required ($P<.003$), as shown in Fig 2. The LF peak frequency was not discernibly affected by effort. As during unconstrained testing, the HF remained constant.

COMMENT

Tremor occurs in patients with a history of alcohol abuse, most often during acute alcohol withdrawal. Prior studies have suggested that the tremor seen during this period is enhanced physiologic tremor.[1-3,7,8] It is reported to be predominantly postural, with a frequency range of 6 to 11 Hz, and is rarely severe.[2-4,7,8]

Studies have shown that the tremor phase is uncorrelated in two outstretched limbs, arguing against a single central pacemaker mechanism.[4] The tremor is characterized by synchronous firing of motor units and is suppressed within minutes by the intrarterial administration of propranolol.[3,9] These findings suggest that the underlying mechanism is related to entrainment of I-A muscle spindle afferents. Animals studies have demonstrated the presence of adrenergic endings in intrafusal fibers of muscle spindles[10]; in the withdrawal state, increased circulating catecholamines may enhance the rate of muscle contraction and reflex-loop response and promote tremor.

It is not known whether the chronic tremor seen in alcoholism represents another stage in the continuum of acute withdrawal tremor, an unmasking of underlying essential tremor, or another disorder due to the toxic effects of alcohol on central and peripheral nervous systems.

Clinical studies indicate that the tremor of chronic alcoholism differs from essential tremor.[4] With the former, there tends to be no family history, a higher frequency range, and less functional disability. It is usually limited to the arms, predominantly postural, and responsive to propranolol therapy.[4] The patients in our study had approximately equivalent postural and kinetic ("static" and "dynamic") amplitudes clinically, and somewhat larger postural components on displacement recording. Of the patients in our study, one of five had a family history of tremor and three of four reported tremor suppression by alcohol and one of two by diazepam. Propranolol was ineffective in the single case in which it was administered.

In this study, we sought to gain an understanding of the underlying mechanism of the tremor of chronic alcoholism and to determine whether examination of the tremor behavior under varying mechanical conditions provided objective data that could distinguish it from tremors with similar clinical characteristics but different underlying causes. The rationale behind the loading schemes chosen was based on established hypotheses of tremor mechanism. Tremors have been attributed to three basic mechanism classes. The central oscillator theory suggests that tremor is driven by an autonomous central source that produces tremor with fixed frequency, torque, and amplitude characteristics, uninfluenced by peripheral factors.[11,12] The biomechanical resonance theory states that a body part oscillates at its "natural" frequency, which is determined by its intrinsic inertial and springlike properties.[13] In this case, frequency will bear an inverse relationship to added limb mass, and tremor should be suppressed by isometrically constraining the limb. The third theory, reflex-loop instability, is based on the potential for autonomous oscillation of segmental as well as transcortical reflex arcs; exaggerated and synchronized neuromuscular transmission delays may produce this tremor.[14]

In this study, two simultaneous tremor peaks were evident in all patients. The HF peak ranged in frequency from 9.4 to 9.6 Hz. Its frequency did not vary discernibly with influence tremor characteristics, we suggest that a central limb loading during unconstrained testing or with effort during isometric testing. Because peripheral factors did not influence tremor characteristics, we suggest that a central oscillator mechanism underlies this tremor component.

The large-amplitude LF peak was the clinically obvious tremor component, with a peak power density range that was four to 36 times greater than that of the HF peak during postural and kinetic activities. The LF component frequency was inversely related to combined load-limb inertia, suggesting a biomechanical tremor mechanism. However, during isometric testing, a situation in which mechanical factors are eliminated, the LF peak was recorded. This finding excludes a purely biomechanical resonance mechanism. In addition, the LF amplitude increased with greater voluntary effort, which is not consistent with a purely central mechanism. These findings therefore seem to implicate reflex-loop instability as well as biomechanical resonance.

Two simultaneous tremor peaks with these load-response properties have been described by Elble[15] in normal controls and in patients with essential tremor. In normal subjects and in those with early essential tremor, he found that the LF peak is the dominant component. As essential tremor worsens, the HF peak was observed to increase, gradually dominating the tremor spectrum.

In the alcoholic patients in this study, the prominent tremor was the LF peak, like the physiologic tremor of Elble's normal subjects. Although LF peak powers differed among patients, the HF peak powers were remarkably consistent, having no apparent relationship to severity of tremor or length of prior alcohol exposure. These findings suggest that the LF peak represents the significant pathologic component of the tremor of chronic alcoholism. It has a biomechanical reflex mechanism, and is similar to normal physiologic tremor.[15,16] We conclude that, as in the case of acute withdrawal tremor, it is primarily an enhanced physiologic tremor.

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Spinal Epidural Abscess

Early Detection With Gadolinium Magnetic Resonance Imaging

Allen J. Teman, MD

• To emphasize the importance of timely diagnosis of spinal epidural abscess, thirteen patients admitted to a single general hospital are presented. In 10 patients, diagnosis was not appreciated at the time of presentation. After treatment, four remained paraparetic and three died. Nine patients had predisposing factors, including seven with infections at sites other than the spinal canal. *Staphylococcus aureus* was the predominant organism. Outcome was equally devastating for the seven patients with acute and the six patients with chronic infections. Gadolinium-enhanced magnetic resonance imaging was the most useful diagnostic test, and we recommend that it be performed promptly in any patient with clinical features suggesting spinal epidural abscess since early surgical drainage and appropriate antibiotics may yield a favorable outcome.

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Prompt diagnosis of spinal epidural abscess (SEA) is imperative because delays in treatment may result in irreversible neurologic impairment or death. To emphasize this and to illustrate the value of gadolinium-enhanced magnetic resonance imaging (MRI) in early diagnosis, 13 patients with acute or chronic SEA are presented. In 10 patients, the diagnosis of SEA was not entertained at presentation. Three died and four remained paraparetic.

SUBJECTS AND METHODS

A computer search of records of a tertiary care suburban general hospital identified 13 patients who were discharged with a diagnosis of SEA between January 1981 and June 1989. Inquiries of attending neurologists, neurosurgeons, and review of surgical pathology records identified no additional cases. The records and roentgenograms of all patients were reviewed. Surviving patients and family members were interviewed when possible. I was directly involved with the care of two patients (cases 1 and 13). Findings in the 13 cases are summarized in Tables 1 and 2, plus two illustrative cases are described in greater detail.

REPORT OF CASES

CASE 1.—A previously healthy 52-year-old man visited the hospital's emergency department complaining of fever, constipation, and midthoracic pain for 2 days. Other than low-grade fever, examination was unremarkable. After an abdominal flat plate revealed large amounts of stool within the colon, he received an enema and was released. He returned 2 days later with similar complaints. Examination revealed right lower quadrant abdominal tenderness and a white blood cell count of 14×10^9/L. Laparotomy was performed, revealing a normal appendix. On the third postoperative day he developed urinary retention. By the fourth day he had a grade 1/5 paraparesis with impaired sensation below the midthoracic level. Gadolinium MRI that day revealed persistence of high signal in the dorsal thoracic epidural space on progressive T2-weighted images with compression of the spinal cord at the level of the eighth thoracic vertebrae (Figs 1 and 2). Purulent material was removed during a decompressive laminectomy that yielded *Staphylcoccus aureus*. He was given cefoxitin, nafcillin, and dexamethasone and power in his legs improved to 4/5. He died of a pulmonary embolism 5 days after spine surgery.

CASE 2.—A 64-year-old woman was hospitalized for neck pain, confusion, and lethargy. She was known to have metastatic breast cancer, and a history of alcohol abuse. One month previously she was treated for 10 days with oral trimethoprim-sulfamethoxazole for an *Escherichia coli* urinary tract infection. After a single dose of ceftazidime administered intravenously, a lumbar puncture was performed to rule out meningitis. Cerebrospinal fluid (CSF) contained 99×10^6/L white blood cells (0.98 polymorphonuclear cells), a glucose level of 1.5 mmol/L (serum glucose, 3.9 mmol/L), and a protein level of 0.96 g/L. The cerebrospinal fluid culture was negative. She then reported weakness of the arms; examination revealed hypoactive upper extremity reflexes and electromyography confirmed a cervical radiculopathy. Cervical spine MRI revealed evidence of epidural inflammation with compression of the spinal cord at the C4 through C6 levels (Fig 3). Because of coexisting coagulopathy, decompressive surgery was not performed. She was given intravenous ceftazidine, ampicillin, ceftriaxone, clindamycin, and gentamicin over 7 weeks, followed by dexamethasone. Her findings resolved and cervical spine MRI at the completion of treatment revealed no evidence of inflammation (Fig 4). Two months later she was readmitted with sepsis and a perforated bowel. Within 24 hours she became acutely quadraplegic and died. An autopsy was not performed.

RESULTS

Patient ages ranged from 44 to 75 years. Seven patients were men and six were women (Table 1). Predisposing factors were present in nine. On initial presentation all

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Table 1.—Patient Data

Patient/ Age, y/Sex	Presenting Symptoms	Predisposing Factors	Duration of Symptoms, d	Delay From Presentation, Until Surgery, d
1/52/M	Back pain, constipation	None	2	9
2/64/F	Neck pain, confusion	Alcohol abuse	3	No surgery
3/70/F	Sciatica, incontinence	None	28	25
4/44/F	Neck pain, arm weakness	Intravenous drug abuse	14	13
5/63/M	Sciatica	Diabetes	14	8
6/59/M	Back pain, leg weakness	Alcohol abuse	2 mo	7
7/68/M	Back pain, paraparesis	Diabetes	2 mo	<24 h
8/74/F	Neck pain	Nadir from chemotherapy	7	Needle biopsy, day 18
9/65/M	Back, chest, and leg pain, constipation	None	7	No surgery
10/75/M	Back pain	Alcohol abuse	3 mo	2 mo
11/58/F	Draining surgical wound	Disk surgery	10*	1
12/52/F	Back pain, paraparesis	Tuberculosis	5 mo	<24 h
13/65/M	Back pain, paraparesis	None	4	4

*This patient presented 10 days after lumbar disk surgery.

Table 2.—Results of Cerebrospinal Fluid Analysis

Patient No.	Glucose, mmol/L	Protein, g/L	Leukocyte Count, $\times 10^9$/L	% Neutrophils	% Monocytes	Culture and Sensitivity
2	1.5	0.96	0.099	0.98	0.02	Negative*
5	4.5	2.5	0.26	0.16	0.84	Negative
6	3.3	1.87	0.017	0	1	Negative
7	6.1	0.3	0.048	0.63	0.37	Negative
8	4.9	0.39	. . .	. . .	. . .	Negative
9	0.3	5.35	7.1	0.92	0.08	Negative
10	. . .	. . .	0.002	0	1	Negative†

*Patient 2 received a single dose of intravenous antibiotic therapy prior to lumbar puncture.

†Antibiotics were given prior to lumbar puncture. Postmortem cerebrospinal fluid cultures yielded *Pseudomonas aeruginosa*, α-hemolytic streptococci, and *Staphylococcus epidermidis*.

complained of back pain, two had sciatica, five had leg weakness, and four had bowel or bladder dysfunction. Duration of symptoms until presentation ranged from 2 days to 5 months, and 54% were admitted within 2 weeks of the onset of symptoms. Time from initial presentation until surgical intervention ranged from hours to 25 days. Eight patients had radiculopathy, and an equal number had myelopathy. Seven were febrile on admission, and seven had serum leukocyte counts above 12×10^9/L. Fifty-four percent had infections at sites other than the spine: four had urinary tract infections, two had a tooth abscess, one had a chest wall abscess, and one had a paravertebral abscess from dehiscence of a surgical anastomosis of the gastroesophageal junction.

Seven infections occupied the thoracic epidural space, three were lumbar, and three were cervical. Osteomyelitis was documented either pathologically or radiographically in 11 patients. Meningitis occurred in two patients. The predominant organism was *Staphylococcus aureus*, and cultures yielded multiple organisms in two patients. A case of Pott's disease that extended into the epidural space is included in this series. Blood cultures were positive in six patients but negative in four, and the remaining patients did not have blood cultures drawn.

Hypoglycorrhachia was present in two of the seven patients who underwent lumbar puncture (Table 2). Cerebrospinal fluid protein ranged from 0.39 to 5.35 g/L, and white blood cell counts ranged from 2 to 7100×10^6/L. Of the five patients with CSF pleocytosis, three were predominantly mononuclear, and two were polymorphonuclear.

Spinal epidural abscess was not included in the initial differential diagnosis in 10 (77%) of 13 patients. This included three of the four patients who were left paraparetic and the three who died. In contrast, two of the three patients initially correctly diagnosed did well.

COMMENT

The incidence of SEA is approximately one of every 20 000 hospital admissions (13 of 271 870). Predisposing factors are diabetes, alcohol abuse, immunosuppression, sepsis, intravenous drug abuse, and back trauma.[1] Spinal surgery and lumbar puncture may seed the epidural space with organisms, and blunt trauma can cause an epidural hematoma that will serve as a nidus for infection from transient bacteremia.

Pathophysiologically the width of the epidural space relates to the probability that an abscess will occur within a certain region of the spine. Cervical abscesses are the rarest, since the epidural space measures approximately 0.1 cm, while the thoracic spine has the greatest width measuring from 0.5 to 0.75 cm.[2] Over a span the epidural space in the regions from T4 to T8 and L2 to L5 are the largest.[3] Also important anatomically is the extensive epidural venous plexus within the thoracic and lumbar spines that provides access for infective organisms.[4]

Typically an SEA will span three to six vertebrae, and have a single epicenter at which spinal cord and nerve root damage will occur.[5] Rarely an SEA will have more than one epicenter or it may span the entire length of the spine.[6] Most infections spread hematogenously to the dorsolateral spine, since ventrally the dura is tightly adherent to the posterior longitudinal ligament. A ventrally located abscess usually extends from an adjacent osteomyelitic focus, and clinically back pain may have been present for a longer

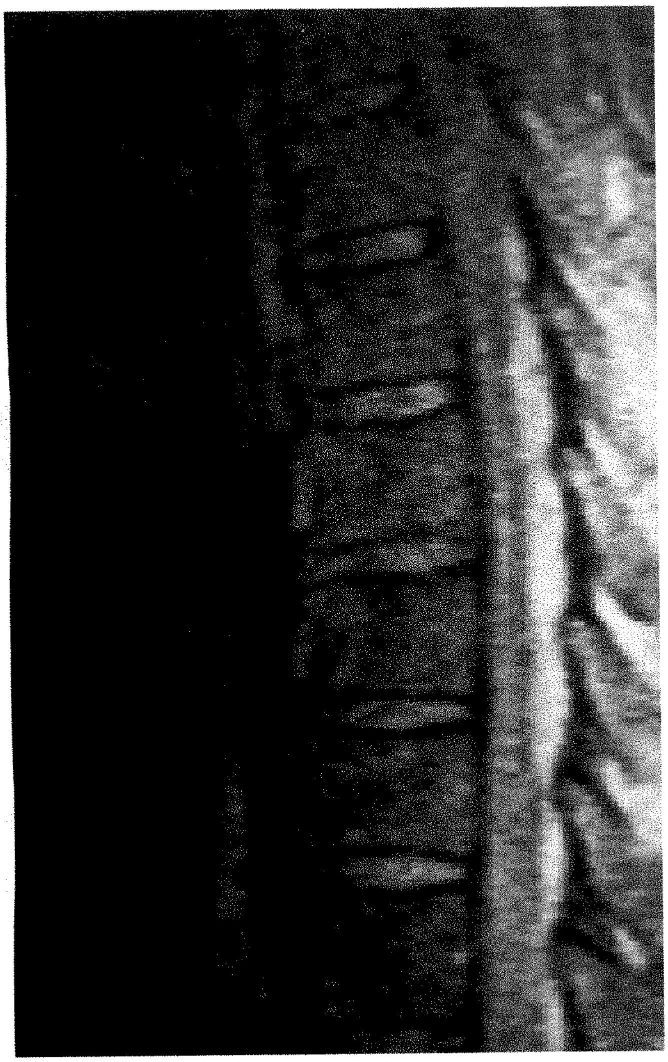

Fig 1.—*T2-weighted sagittal magnetic resonance imaging revealed persistent high signal in the dorsal aspect of the spinal canal from T6 to T10. In the normal spine as images become progressively more T2 weighted the signal intensity eminating from epidural fat decreases.*

period of time prior to the onset of neurologic dysfunction.[7,8]

Cerebrospinal fluid usually reveals an elevated protein concentration and a mononuclear pleocytosis with a normal glucose concentration. Bacterial meningitis is rare, since the dura acts as a barrier against the passage of organisms into the CSF. One must be aware that inadvertent puncture of an SEA may lead to CSF seeding.

Magnetic resonance is the best imaging study for confirmation of the diagnosis and follow-up, since signal characteristics of various tissues give clues to the cause of the disease process in addition to providing anatomic information.[9] Magnetic resonance imaging allows direct visualization of the intervertebral disks, spinal cord, and soft tissues. Gadolinium readily enhances actively inflammed tissues and defines anatomic boundaries. Abnormal signal within the disk space points toward the possibility of infection.

Patients with bacterial meningitis should have myelography performed in conjunction with computed tomography, since MRI poorly distinguishes the subarachnoid space from the infected epidural tissue.[1] The drawbacks of myelography include the inadvertent seeding of the CSF with bacteria during lumbar puncture; the inability to define the upper and lower borders of an SEA in patients with complete block of CSF flow; and the clinical deterioration that may occur after removal of spinal fluid in patients with a complete CSF block.

Treatment of SEA is usually surgical, although nonsurgical approaches have been reported.[10] Most authors are in

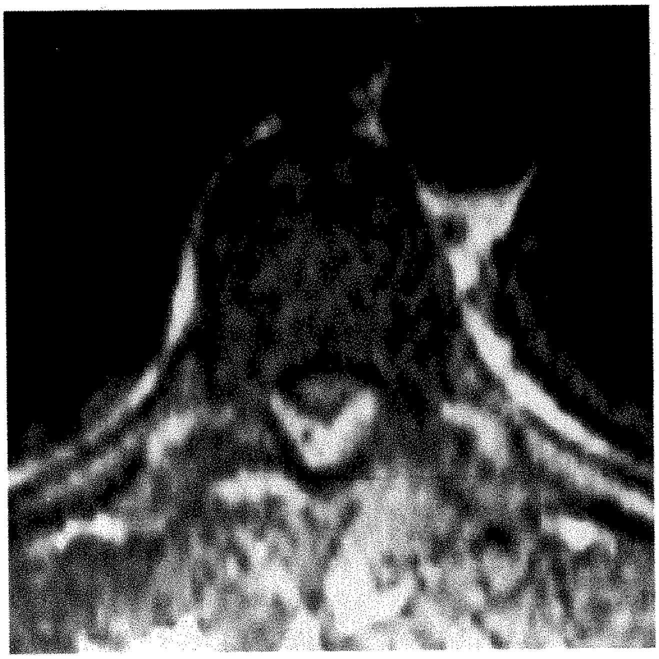

Fig 2.—*Axial T1-weighted image at the T8 level reveals marked cord compression from the dorsal epidural abscess.*

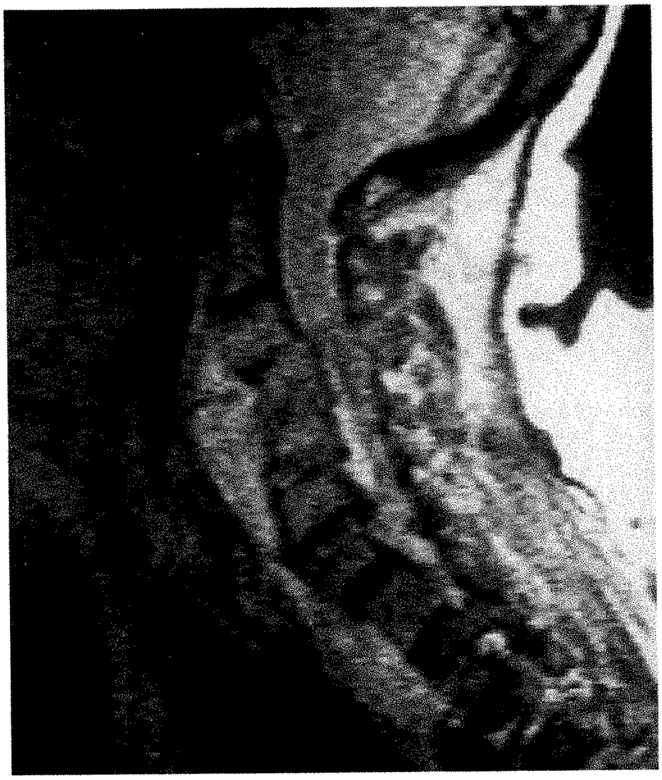

Fig 3.—*Sagittal T2-weighted magnetic resonace imaging reveals ventral epidural abscess with cord compression (T2, 2500 milliseconds; TE, 76 milliseconds).*

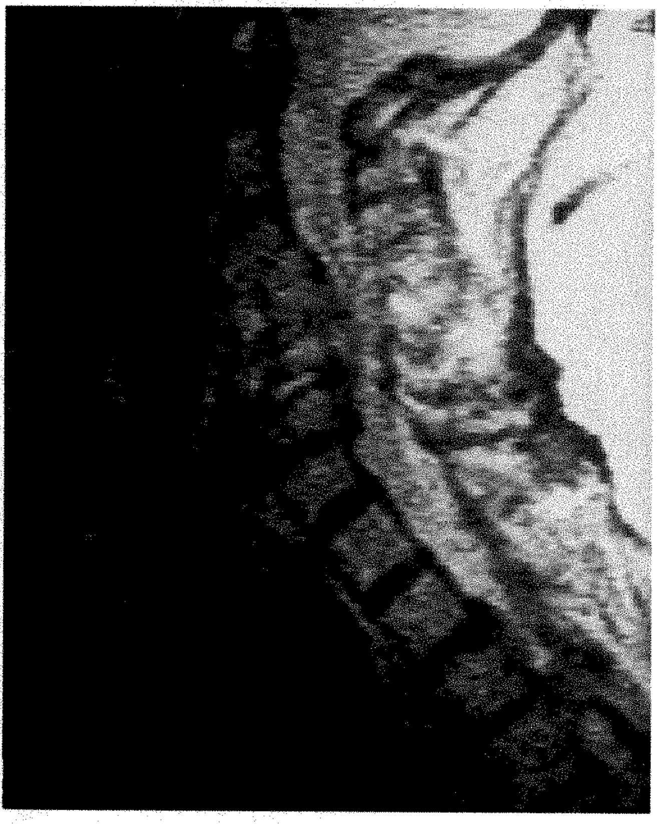

Fig 4.—*After treatment T2-weighted image shows resolution of high signal eminating from ventral epidural space (TR, 2500 milliseconds; TE, 76 milliseconds).*

favor of acute surgical intervention after obtaining radiologic confirmation of the diagnosis, although in this study two patients were treated without surgery. One patient did well but the other died. Surgery can be used to obtain cultures and remove infected material from vascular channels within the epidural space. Removal of infected material and bone will help prevent or alleviate spinal cord compression. Surgery should be performed promptly in all patients except those unable to survive an operation. Patients who are plegic for more than 72 hours may be managed conservatively.[11] In such cases needle biopsy may be used to provide culture material, and MRI to follow the response to treatment. Antibiotic treatment should be directed against both gram-positive and gram-negative organisms until cultures are reviewed. A logical choice would be the combination of a penicillinase-resistant penicillin with either a third-generation cephalosporin or an aminoglycoside. First- and second-generation cephalosporins should not be used due to their poor CSF penetration, and reports exist of the development of bacterial meningitis during their use.[12,13] Four weeks of intravenous antibiotic therapy is sufficient to treat an SEA although when osteomyelitis is present treatment should be administered for 6 to 8 weeks.[14] Although *Staphylococcus aureus* is the most common organism, intravenous drug abusers as well as patients with gastrointestinal or genitourinary foci have a high propensity for gram-negative infections.[13,15]

The rarity of SEA contributes to its likelihood to be overlooked. Patients with back pain and a history of a febrile illness dating back weeks to months may be harboring a chronic SEA. Chronic and acute abscesses can be equally devastating. Heusner's[8] theory that the chronic "syndrome unfolds at a leisurely pace that almost assures the patient of operation before paralysis is complete or neurologic damage irreversible" is false. I believe the mechanism by which patients with a chronic SEA suddenly deteriorate is by vascular compromise, as demonstrated in one of my patients whose MRI performed immediately after onset of acute paresis revealed absence of cord compression. Venous infarction was suspected, since dysfunction of the posterior columns accompanied weakness and loss of spinothalamic sensations. Note that all pathologic specimens contained a mixture of acute and chronic inflammatory cells.

Physicians should maintain an index of suspicion of SEA in any patient with back pain and a history of a febrile illness. Immunocompromised patients pose additional cause for concern. Patients suspected to harbor an SEA require urgent radiologic confirmation, preferably by gadolinium MRI, followed by surgical drainage and antibiotic therapy.

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Further Observations on the Pathology of Subcortical Lesions Identified on Magnetic Resonance Imaging

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• We performed postmortem magnetic resonance imaging and pathologic examinations on the brains of seven consecutive patients older than 50 years of age who died of nonneurologic causes. Multiple hyperintense subcortical lesions were identified in each patient, and a total of 29 lesions were examined histologically (eight rims, six caps, six punctate lesions, and nine patches). Rims were characterized by subependymal gliosis and loss of the ependymal lining; caps were associated with myelin pallor, gliosis, and arteriosclerosis; punctate lesions were characterized by dilated perivascular spaces and perivascular gliosis; and patches were associated with myelin pallor and dilated perivascular spaces. The pattern of myelin pallor defined the size and shape of caps and patches. Arteriosclerosis was identified in six of six caps, three of six punctate lesions, and in three of nine patches. These data indicate that (1) each type of hyperintense subcortical lesion has a distinct pathologic correlate; (2) arteriosclerosis is not invariably associated with all types of hyperintense subcortical lesions on magnetic resonance imaging; and (3) myelin pallor appears to contribute to the magnetic resonance imaging signal at 1.5 tesla.

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The causes and clinical significance of hyperintense subcortical lesions (HSL) identified on magnetic resonance imaging (MRI) of the brain in the elderly are uncertain.[1,2] Many etiologic factors have been proposed, including normal aging,[3,4] subcortical ischemia,[5,6] normal pressure hydrocephalus,[7] and cerebral edema.[8] Reported clinical associations include dementia (Binswanger's disease), pseudobulbar palsy, gait difficulties, and urinary incontinence[5,9-11]; however, it has also been suggested that HSL are of doubtful clinical significance.[3]

Clarification of the causes and clinical significance of HSL on MRI may be enhanced by studying the histopathologic correlates of these lesions. A few postmortem studies[4,6,12-16] have shown that several histologic processes are associated with these radiologic lesions. These include dilated perivascular spaces (état criblé),[6,13] arteriosclerosis,[6,16] partial loss of myelin and axons,[12,16] gliosis,[14,15] lacunar infarction,[12,14] and congenital diverticula.[14] One study,[4] however, did not find any correlation between hyperintense lesions in the centrum semiovale and pathologic features.

This study was undertaken to delineate further the pathologic correlates of HSL on MRI. Our specific aims were to determine (1) if each type of HSL on MRI (ie, rims, caps, punctate lesions, and patches) has a distinct pathologic correlate; (2) the association, if any, of arteriosclerosis to HSL on MRI; and (3) the relative contribution of each histologic process (eg, gliosis, edema, and myelin pallor) to hyperintense signal on T_2-weighted MRI.

PATIENTS AND METHODS

Patient Selection

Consecutive patients older than 50 years of age who died of nonneurologic causes, and on whom a full postmortem examination was performed between August 1988 and April 1989 at the Cleveland (Ohio) Clinic Foundation, were considered for the study. Patients with nonvascular diseases known to affect the periventricular white matter (eg, multiple sclerosis, inherited leukodystrophies, human immunodeficiency virus infection, progressive multifocal leukoencephalopathy, and radiation necrosis) were excluded. Other exclusion criteria were previous brain surgery or trauma and artificial ventilation of a brain-dead patient for longer than 24 hours.

MRI Protocol

Postmortem MRI of the brains of these patients was performed using the technique described previously by Awad et al.[5] After fixing in a 20% formalin solution for 1 to 2 weeks, the brains were placed in a plastic container, small enough to fit within the head compartment of the MRI unit. The brains were immersed in fresh water, and ventricular air was evacuated through the foramina of Luschka and Magendie by tilting the brain. The container was oriented in the head compartment to align the sagittal sulcus with the sagittal scanning plane of the MRI. Using a 1.5-tesla MRI unit, scanning was performed in the axial, sagittal, and coronal planes with 1-cm-thick sections. A multiple spin echo protocol to generate a slightly T_2-weighted image (TR = 2000 milliseconds, TE = 25 milliseconds) and a standard clinical protocol to generate a heavily weighted T_2 image (TR = 2000 milliseconds, TE = 80 milliseconds) were used for each brain.

The HSL on MRI were localized in at least two planes, and they were classified as one of four types: (1) rim, a thin line less than 2 mm thick of hyperintensity surrounding the lateral ventricles (a brain could have more than one rim if the line of hyperintensity

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Table 1.—Clinical and Postmortem Findings in Seven Patients Undergoing Postmortem MRI*

Patient No./ Age, y/Sex	Vascular Risk Factors	Pertinent Medical History	Carotid and Intracranial Arteries	Cardiac Pathology	Brain Weight, g†	Gross Brain Pathology
1/73/F	Hypertension	Myocardial infarction (1987) recurrent syncope, post-CABG arryhthmias, and hypotension preceding death	Mild plaque of internal carotids	Heart weight,‡ 700 g; LV thickness,§ 1 cm; subendocardial infarctions of septum; severe CAD	1610	Normal
2/64/F	Diabetes mellitus, 40-60 pack-year smoking	Carcinoma of breast, congestive heart failure, MVR and CABG, postoperative renal failure, and pericarditis	Normal	Heart weight, 540 g; LV thickness, 1.6 cm; severe CAD	1290	Normal
3/66/M	None	Myocardial infarction (1978) renal cell carcinoma, interferon and interleukin therapy	Normal	Heart weight, 440 g; LV thickness, 1.6 cm; moderate CAD	1325	Normal
4/71/F	Hypertension, diabetes mellitus, 30 pack-year smoking	Crohn's disease, syncope, pacemaker for sick sinus syndrome, L hemisphere TIA, mild dementia, partial excision of small bowel, sepsis, hypotension	70% L internal carotid stenosis	Heart weight, 500 g; LV thickness, 1.3 cm; mild CAD	1100	L occipital infarct, R thalamic lacunae
5/55/M	30 pack-year smoking	Metastatic lung carcinoma	Normal	Heart weight, 260 g; LV thickness, 1.2 cm; normal coronary arteries	1370	Normal
6/73/M	Hypertension, diabetes mellitus, prior smoking history	Myocardial infarct (1977), congestive heart failure, L occipital infarct (1986), aortic aneurysm repair, postoperative hypotension preceding death	Atherosclerosis of intracranial arteries	Heart weight, 770 g; LV thickness, 1.3 cm; thrombus in LV; LV infarct; severe CAD	1150	L occipital and temporoparietal infarcts
7/74/F	Hypertension	Atrial fibrillation, mild dementia, syncope, renal failure, one seizure, sudden death	Not available	Heart weight, 490 g; LV thickness, 2.2 cm; 90% stenosis of anterior descending artery; aortic stenosis	1340	Normal

*MRI indicates magnetic resonance imaging; CABG, coronary artery bypass graft; LV, left ventricle; CAD, coronary artery disease; MVR, mitral valve replacement; and TIA, transient ischemic attack.

†Normal, 1240 to 1680 g (male); 1130 to 1510 g (female).

‡Normal, 325±75 g (male); 275±75 g (female).

§Normal, 8 to 15 mm.

was not continuous); (2) cap, hyperintense signal less than 5 mm thick around a pole of a lateral ventricle; (3) punctate lesion, a dotlike signal of hyperintensity in the subcortical region (gray or white matter); and (4) patch, a nonpunctate area of hyperintensity in a subcortical region that was not adjacent to the ventricular surface (a patch could be independent of, or contiguous with, a cap).

Brain Cutting and Pathologic Examination

At autopsy, both carotid bifurcations and the entire circle of Willis were evaluated grossly for the presence of atherosclerosis. Routine histopathologic studies of the internal carotid arteries were performed. The heart was evaluated using standard pathologic techniques looking for evidence of hypertension (heart weight, left ventricular thickness), heart failure (cardiomyopathy, size of atrium and ventricles), valvular heart disease, and coronary artery disease. Other major arteries were also evaluated for the presence of atherosclerosis.

After postmortem MRI, the brains were weighed and cut in the same axial planes used for MRI. Ventricular size was evaluated by measuring the linear span of the anterior bodies of the lateral ventricles just above the head of the caudate nucleus, proximal to the diverging anterior horns.[7] Large tissue sections (0.5 to 1 × 3 × 3 cm) of each area harboring an MRI lesion were taken. Additional sections were taken from the hippocampus bilaterally for detection of Alzheimer's plaques and tangles. The sections were embedded in paraffin, after which several serial sections 6 to 10 μm thick were taken every 250 to 500 μm. Contiguous sections were processed with a modified Kluver-Barrera stain for routine histologic examination, glial fibrillary acidic protein stain

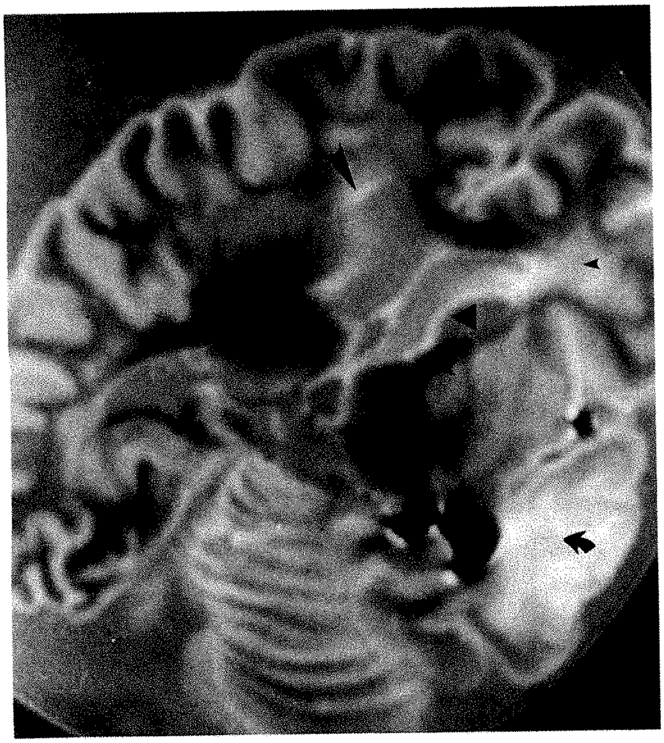

Fig 1.—*Partially T_2-weighted magnetic resonance imaging of the brain of patient 6, showing rims (solid triangle), caps (large arrowhead), punctate lesions (medium arrowhead), prominent patches (small arrowhead), and left temporal infarct (curved arrow).*

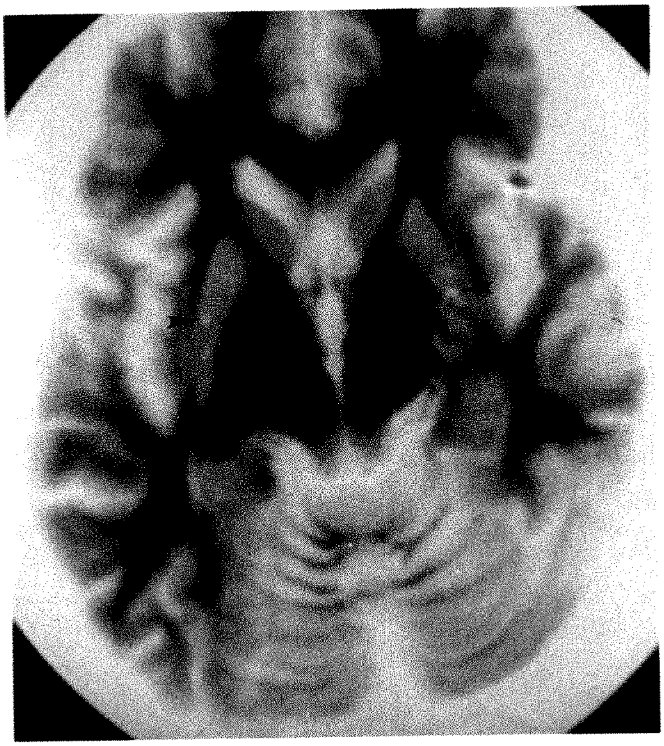

Fig 2.—*Partially T_2-weighted MRI of the brain of patient 2, showing prominent punctate lesions (arrowheads).*

Table 2.—Histologic Features of Rims, Caps, Punctate Lesions, and Patches*

	Rims (n=8)		Caps (n=6)		Punctate Lesions (n=6)		Patches (n=9)	
Histologic Feature	**Within Rims**	**Normal Ventricular Surface**	**Within Cap**	**SA With Normal MRI Signal**	**Within Punctate**	**SA With Normal MRI Signal**	**Within Patch**	**With Normal MRI Signal**
Dilated perivascular spaces	0	0	2	4	6†	3	9	8
Arteriole venous ectasia	0	0	0	0	4	0	0	0
Arteriosclerosis (thickening of arteriole wall)	0	0	6	1	3	1	3	0
Myelin pallor	0	0	6†	0	0	1	9†	0
Parenchymal edema	0	0	0	1	0	0	7	5
Inflammation	0	0	1	1	2‡	0	4§	4
Gliosis	8†	0	6	0	6‡	2	6	0
Amyloid angiopathy	0	0	0	0	0	0	0	0

*SA indicates surrounding area; MRI, magnetic resonance imaging. Plaques and tangles not identified in any of the hippocampal sections of the seven brains. A few senile plaques identified in left frontal cortex of patient 4.

†Major feature.

‡Perivascular.

§Macrophage infiltration.

for astrocytes and their processes, Congo red stain for amyloid, and a monoclonal antibody stain to desmin that highlights smooth muscle fibers in blood vessels.

Because of the large number of lesions identified on MRI, only slides of sections taken from areas harboring prominent MRI lesions were examined. A neuropathologist (M.L.E.) graded the following histologic features as present or absent: myelin pallor, gliosis, inflammation, parenchymal edema, amyloid angiopathy, Alzheimer's plaques and tangles, arteriosclerosis, arteriolar ectasia, and enlarged perivascular spaces. Arteriosclerosis within a cap or patch was considered present if more than one third of the arterioles in the lesion had thickened walls with luminal compromise.

For all caps, patches, and punctate lesions, the histologic features of the tissue corresponding to the MRI lesion were compared with the histologic features of the surrounding white or gray matter that had normal signal on MRI. Additionally, the histologic features of the ependymal lining and subependyma in regions corresponding to rims on MRI were compared with the histologic features of the ventricular surface in regions that showed normal signal on MRI.

RESULTS

The clinical data and postmortem findings in seven patients who qualified for the study are shown in Table 1. Six

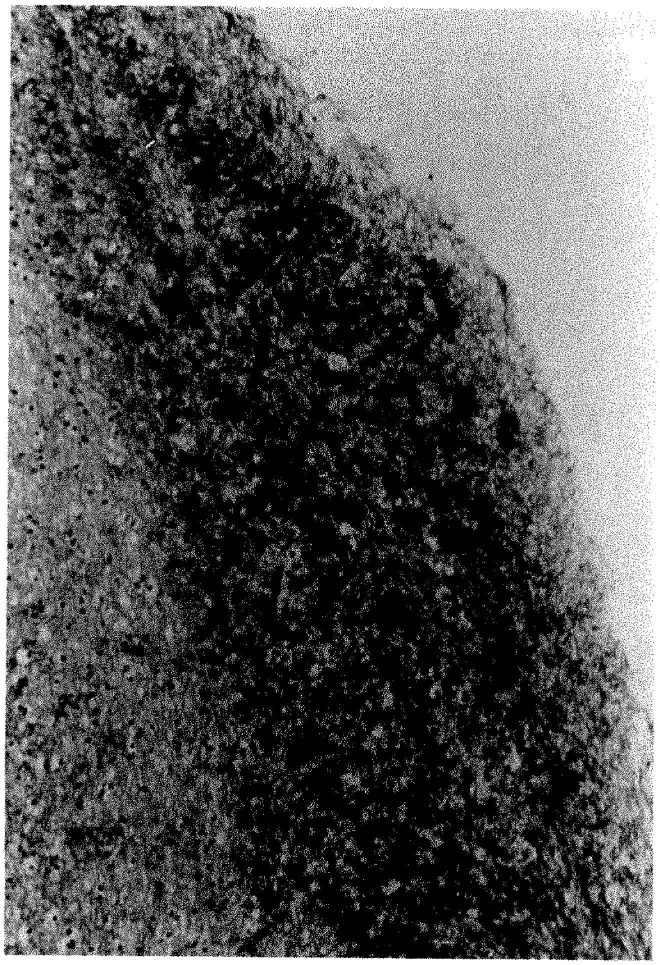

Fig 3.—*Subependymal gliosis was the pathologic correlate of all rims on magnetic resonance imaging (glial fibrillary acidic protein stain, original magnification × 100).*

patients had at least one vascular risk factor; five had moderate or severe coronary artery disease; five had a history of congestive heart failure, syncope, or hypotension; two had large artery occlusive cerebrovascular disease and associated cortical infarctions; and two patients were mildly demented.

The heart weight was above normal in six patients, and left ventricular thickness was increased in three patients. The brain weight was below normal in two patients (one of whom was mildly demented), and the cerebral ventricles were of normal size in all patients. The ventricular span in all patients was less than 3.3 cm (the upper limit of normal for subjects over the age of 60 years is 4.1 cm).[7]

All patients had multiple HSL on MRI. Three patients had rims, caps, punctate lesions, and patches (Fig 1); two patients had rims, caps, and punctate lesions without patches; and the other two patients had caps, punctate lesions, and patches without rims. Rims and caps were found predominantly around the frontal horns, and punctate lesions occurred predominantly in the basal ganglia (Fig 2). Of 16 patches, nine were located in the frontal lobes, three in the occipital lobes, two in the parietal lobes, and two patches overlapped the parieto-occipital lobes.

The histologic features of 29 prominent HSL on MRI are shown in Table 2. Rims were characterized pathologically by subependymal gliosis (Fig 3), which was invariably associated with loss of the ependymal lining. The ventricular surface in regions with normal signal on MRI showed normal ependymal lining without evidence of subependymal gliosis. For the other types of HSL on MRI (ie, caps, punctate lesions, and patches), at least two histologic features occurred more frequently within each lesion type than in adjacent tissue with normal signal on MRI (Table 2). However, the size and shape of each type of HSL on MRI were defined uniquely by a single histologic feature, ie, the pattern of myelin pallor defined the morphology of caps and patches (Fig 4), and dilated perivascular spaces defined the morphology of punctate lesions (Fig 5).

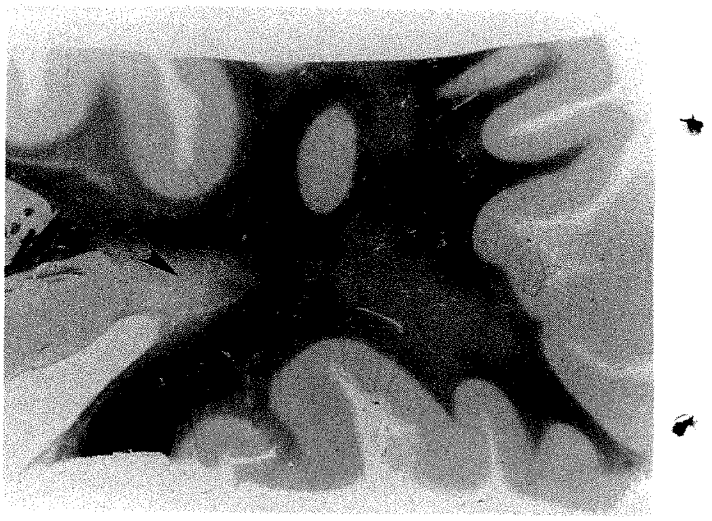

Fig 4.—*The size and shape of the cap (large arrowhead) and patch (small arrowheads) are defined by the pattern of myelin pallor (Kluver-Barrera stain, original magnification × 10).*

Arteriosclerosis occurred more commonly within caps and patches than in adjacent tissue with normal signal on MRI (Table 2); however, thickening of numerous vessels was present in only three of nine patches that were examined.

COMMENT

Classification systems have been proposed to grade the different types of HSL identified on MRI in the elderly.[17,18] These systems suggest that rims and caps may be precursors of irregular lesions extending from the ventricular surface into the deep white matter and that punctate lesions may be the precursors of isolated white matter patches. A corollary of this concept is that rims, caps, punctate lesions, and patches are part of a pathophysiologic continuum.

Our results indicate that each type of HSL had a distinct histologic correlate, which suggests that a common cause for all HSL on MRI is unlikely, unless the pathologic response of each subcortical region to a common insult is distinctive.

Each of the seven patients in our study had small frontal caps that are considered normal by some authors.[19,20] Leifer et al[19] suggest that the pale staining areas of finely textured myelin and axons that characterize small caps constitute the subcallosal fasciculus, a normal anatomical pathway. Larger caps with irregular borders extending into the deep white matter were not present in any of our patients. The histologic appearance of these lesions, which are identified in some elderly patients with hypertension, requires further study.

Five of our seven patients had thin rims on MRI that were characterized histologically by subependymal gliosis

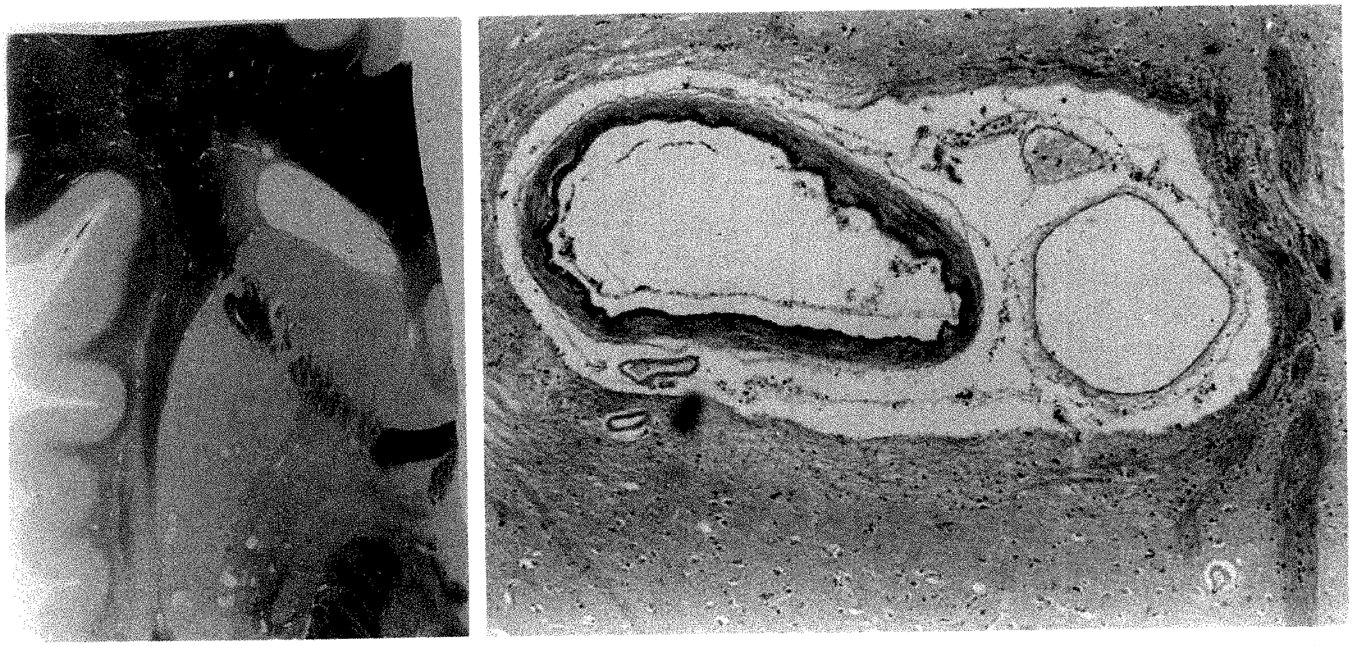

Fig 5.—*Left, Multiple dilated perivascular spaces surrounding arterioles in the basal ganglia. Right, The larger dilated perivascular spaces correlated with punctate lesions on magnetic resonance imaging (Kluver-Barrera stain, original magnifications ×10 [left] and ×200 [right]).*

associated with loss of the ependymal lining. These findings suggest that the pathophysiology of rims may be related to the ventricular system and the dynamics of cerebrospinal fluid.

One theory that attempts to link rims, caps, and patches is that normal pressure hydrocephalus may lead to breakdown of the ependyma, reactive subependymal gliosis (rims), transependymal movement of cerebrospinal fluid into the periventricular region, and secondary pathologic changes in the white matter (caps and patches).[7,21] The absence of enlarged ventricles in all our patients and the presence of patches without rims in two of seven patients suggest that normal pressure hydrocephalus was not the cause of lesions identified on MRI in our patients.

There are accumulating epidemiologic, cerebral blood flow, and pathologic data to suggest that patches on MRI in elderly patients may be caused by subcortical ischemia. Risk factors that are consistently associated with patches are hypertension,[22-24] diabetes,[24] and ischemic stroke.[22,25] Studies using xenon-enhanced computed tomography[24,26] and positron emission tomography[27] have shown diminished subcortical and cortical blood flow in patients with white matter signal abnormalities on MRI.

Pathologic studies have linked arteriosclerosis,[12,16] amyloid angiopathy,[28,29] and sclerosing vasculopathy[30] to patches on MRI. Recently, Van Swieten et al[16] found that elderly patients with HSL on MRI had a significantly higher mean ratio of cerebral arteriole wall thickness to arteriole diameter than did patients with normal white matter.

The results of our study are not inconsistent with the theory that patches are caused by subcortical ischemia. Although numerous thickened arterioles were associated with only three of nine patches examined, prolonged hypotension, congestive heart failure, or syncope was documented in four of five patients with patches on MRI. One patient with patches on MRI (patient 5) did not have arteriosclerosis or a history of hypotension, congestive heart failure, or syncope, which suggests that subcortical ischemia is not the only cause of patches on MRI in the elderly. Amyloid angiopathy was not found in any cortical or subcortical sections that were taken from the seven brains in our study. It is possible, however, that amyloid may have been present in leptomeningeal vessels or other cortical regions that we did not examine.

It is uncertain why only some patients with patches are symptomatic. Perhaps the explanation lies in the underlying histologic features of patches. We found that the histologic features of patches (myelin pallor interspersed with gliosis and dilated perivascular spaces) were remarkably consistent from patch to patch and from patient to patient. Other authors have found additional pathologic features, including lacunar infarctions,[14] areas of necrosis in the white matter,[12] and axonal loss.[12,16] Currently, MRI cannot distinguish between the various histologic features that may underlie patches.

The histologic correlate of punctate lesions, which were found in all our patients, is dilatation of perivascular spaces. It is unlikely that patches represent the confluence of punctate lesions because patches are found in the deep white matter, while punctate lesions are found in the basal ganglia predominantly. Furthermore, confluence of perivascular spaces is not the characteristic histologic feature of patches.

The relative contribution of each histologic feature to increased signal on MRI is uncertain. Ormerod et al[31] have suggested that myelin loss per se has little effect on MRI signal, and that gliosis may underlie the signal abnormalities associated with HSL. In our study, the distribution of myelin pallor defined quite precisely the morphology of caps and patches on MRI, whereas the distribution of gliosis (loosely interspersed in the lesions) did not correspond with the morphology of caps and patches on MRI. These findings suggest that myelin loss is associated with increased signal on MRI, probably on the basis of an increase in fluid-filled extracellular space that accompanies myelin loss.[31]

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CORRECTION

Transposed Words

In the article entitled "Astrocyte Expression of Major Histocompatibility Complex Gene Products in Multiple Sclerosis Brain Tissue Obtained by Stereotactic Biopsy" published in the December issue of the ARCHIVES (1991;48:1244-1246), two words were transposed. On page 1245, the right column, the sentences beginning on lines 11 through 17 should have read as follows: "Numerous astrocytes also demonstrated perinuclear cytoplasmic GFAP positivity. In some cases, individual cells contained in two serial sections could be identified as manifesting reactivity with HLA-DR antisera."

Meningiomas Are Not Significantly Associated With Breast Cancer

Daniel H. Jacobs, MD; Frederick F. Holmes, MD; Michael J. McFarlane, MD

• We studied 283 meningiomas seen at the University of Kansas, Kansas City, from 1948 through 1984, identifying all additional nonmeningeal malignancies and primary brain tumors in these patients and calculating the expected number of additional tumors by the use of a person-year method from age and sex-matched cancer incidence data. We determined expected numbers of total neoplasms in our meningioma population as well as the expected numbers in each major organ system for the sexes independently and together. We then calculated standard morbidity ratios and 95% confidence intervals for each tumor type. The number of breast cancers did not reach statistical significance. We found a significantly increased number of second primary brain tumors in women (standard morbidity ratio, 8.0; 95% confidence interval, 2.2 to 20.4) and an increased number of thyroid cancers in both sexes (standard morbidity ratio, 7.5; 95% confidence interval, 1.5 to 21.9).

(*Arch Neurol.* 1992;49:753-756)

Breast cancer and meningioma occurring as multiple primary tumors in a single individual have been described.[1-5] Whether the association between these two tumors is fortuitous or a true predilection for multiple primary tumors in meningioma or breast cancer patients is unknown. This study analyzes the occurrence of additional primary tumors in a series of patients with meningioma seen at a midwestern university hospital over a 36-year period.

MATERIALS AND METHODS

The records of 283 patients with intracranial meningioma were reviewed. These cases included 177 women and 106 men in whom meningioma was diagnosed at the University of Kansas Medical Center, Kansas City, from 1948 through 1984. The cases were identified from the Kansas University Medical Center Tumor Registry and the Kansas Cancer Data Service, the state tumor registry. The diagnoses were confirmed from the hospital records and the pathology reports contained therein. Data were obtained from hospital records and the tumor registries on the occurrence of additional neoplasms over the lifetimes of these patients with meningioma.

Tables were then constructed to compare these data with standard age- and sex-matched populations derived from the Department of Health, Education and Welfare publication, *Third National Cancer Survey*,[6] for the 3-year period 1969 through 1971. The chosen period falls approximately at the midpoint of our study. The person-years at risk were calculated from birth until death or the last follow-up of each patient with meningioma. The person-years at risk were divided into 5-year age brackets (thus, a 14-year-old would contribute 5 person-years in each of three brackets of 5 years: 0 to 4, 5 to 9, and 10 to 14 years). The total number of person-years in each age bracket representing all patients with meningioma were multiplied by the population-based incidence of cancer in that age bracket, as given by the reference data from the *Third National Cancer Survey*. The product of the two gives *e*, which is the expected number of neoplasms in that age bracket. The sum of *e*s from all of the age brackets gives the expected number of tumors in the study population of patients with meningioma. The data were stratified by sex, and also calculated for the sexes together. An expected number of tumors *e* was calculated for all tumors as well as for tumors originating in particular organ systems (eg, breast or gastrointestinal). 95% confidence intervals (CI) were then calculated for all tumors and for each tumor type, comparing men, women, and all subjects. The 95% CIs were expressed in terms of the standard morbidity ratio (SMR), a ratio of the observed to expected number of neoplasms. The inclusion of unity within the 95% CIs means that the results could have occurred by chance.

Since the Kansas Cancer Data Service episodically surveyed all former Kansas patients with cancer, it is unlikely that we missed any subsequent cancers occurring outside of the state of Kansas. Follow-up data are detailed under the "Results" section. Since the Department of Health, Education, and Welfare data gave incidence data for sexes individually and for sexes together, we followed their example in our calculation of expected numbers of cancers (Tables 1 through 3). Consequently, the expected values in Table 3 are slightly different from the sum of the expected values in Tables 1 and 2. Our report excludes patients who had neurofibromatosis, since these patients are at risk for multiple types of tumors. We analyze other tumors according to the availability of reference data. Following the Department of Health, Education, and Welfare format, we include all malignancies except basal cell carcinoma and squamous cell carcinoma of the skin. Among nonmalignant tumors, we include primary brain tumors, but we exclude all others.

RESULTS

Two hundred eighty-three patients with meningioma were studied, including 177 women and 106 men. Of these

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Table 1.—Occurrence of Second Primary Neoplasms in 277 Women With Meningioma From the University of Kansas Medical Center, 1948-1984*

Tumor Type	No. Observed/ No. Expected†	SMR	95% CI
All types	37/29.3	1.26	0.889-1.701
Breast	12/8.4	1.43	0.738-2.495
Female genital	10/6.5	1.54	0.738-2.829
Gastrointestinal	5/6.2	.81	.262-1.882
Primary CNS	4/0.5	8.00	2.180-20.484‡
Thyroid	2/0.6	3.33	0.404-12.041
Respiratory	1/1.8	0.56	0.014-3.095
Melanoma	1/0.5	2.00	0.051-11.143
Hematopoietic	2/1.6	1.25	0.151-4.515

*SMR indicates standard morbidity ratio; CI, confidence interval; and CNS, central nervous system.

†Expected rates calculated from the *Third National Cancer Survey*.[6]

‡Reached significance.

Table 2.—Occurrence of Second Primary Neoplasms in 106 Men With Meningioma From the University of Kansas Medical Center, 1948-1984*

Tumor Type	No. Observed/ No. Expected†	SMR	95% CI
All types	13/17.1	0.76	0.404-1.300
Gastrointestinal	5/4.4	1.14	0.369-2.652
Primary CNS	2/0.4	5.00	0.606-18.062
Thyroid	1/0.1	10.00	0.253-55.716
Respiratory	2/4.4	0.45	0.055-1.642
Melanoma	1/0.3	3.33	0.0843-18.572
Hematopoietic	0/1.3	0	0-2.838
Genitourinary (prostate)	1/2.6	0.38	0.0097-2.143

*SMR indicates standard morbidity ratio; CI, confidence interval; and CNS, central nervous system.

†Expected rates calculated from the *Third National Cancer Survey*.[6]

‡Reached significance.

Table 3.—Occurrence of Second Primary Neoplasms in 283 Men and Women With Meningioma From the University of Kansas Medical Center, 1948-1984*

Tumor Type	No. Observed/ No. Expected†	SMR	95% CI
All types	50/47.2	1.06	0.786-1.397
Breast	12/6.8	1.76	0.912-3.083
Gastrointestinal	10/11.1	0.90	0.432-1.657
Primary CNS	6/0.9	6.67	0.330-1.958
Thyroid	3/0.4	7.50	1.547-21.918‡
Respiratory	3/7.4	0.41	0.084-1.184
Melanoma	2/0.8	2.50	0.303-9.031
Hematopoietic	2/3.8	0.53	0.064-1.900

*SMR indicates standard morbidity ratio; CI, confidence interval; and CNS, central nervous system.

†Expected rates calculated from the *Third National Cancer Survey*.[6]

‡Reached significance.

patients, 85 (30%) died of their meningioma with an average survival of 2.0 years from diagnosis of meningioma (range, 0 to 19 years). Seventy-two patients (25%) died of other causes, with an average survival from diagnosis of meningioma of 6.8 years (range, 0 to 27 years). Ninety patients (32%) survived with their meningiomas to the end of the study period, with an average length of follow-up of 15.1 years (range, 0 to 36 years). Thirty-six patients (12.7%) were eventually unavailable for follow-up after having been followed up for an average of 10.7 years (range, 0 to 36 years). Four of these 36 patients (1.4%) did not have any follow-up data available.

Of the 283 patients with meningiomas, 42 had 50 additional neoplasms. The specific additional neoplasms that we observed included 12 breast cancers, 10 female genital cancers, 10 gastrointestinal cancers, six brain tumors, three cancers each of the thyroid and lung, two hematopoietic malignancies, two melanomas, one carcinoma of the prostate, and one carcinoma of unknown primary site.

Among 177 women with meningiomas, 37 had additional tumors (Table 1) that included 12 breast cancers, ten female genital cancers (five of corpus uteri, three of cervix, one of ovary, and one of vagina), four primary brain tumors, five colon cancers, two thyroid cancers, two hematopoietic malignancies, one lung cancer, and one malignant melanoma. Among 106 men (Table 2), 13 were found to have additional neoplasms, including five gastrointestinal cancers (one cancer each of cecum, appendix, esophagus, and stomach and one carcinoid of the ileum), two lung cancers, one thyroid cancer, one prostate cancer, two primary brain tumors, and one unknown primary cancer.

In women with meningiomas, tumors of the central nervous system occurred at a significantly higher rate (SMR, 8.00; 95% CI, 2.180 to 20.484). The occurrence of breast cancer in women did not reach statistical significance (SMR, 1.43; 95% CI, 0.738 to 2.495). In men with meningioma, no other tumor type occurred at a significantly increased rate.

In all subjects (Table 3), the number of total neoplasms observed did not exceed chance. Among specific tumor types, the number of breast cancers did not exceed chance (SMR, 1.76; 95% CI, 0.912 to 3.083). However, the number of thyroid cancers significantly exceeded that expected (SMR, 7.50; 95% CI, 1.547 to 21.918). No other tumor type occurred at a frequency significantly greater than expected.

Among the six patients with meningiomas and other primary brain tumors, the four women had clinically significant meningioma, ie, detected during life (Table 4), and two men had clinically insignificant meningiomas, noted incidentally at necropsy. The other primary brain tumors were diverse in type, including two glioblastomas, an ependymoma, an anterior pituitary tumor, a posterior pituitary granular cell tumor, and a brain-stem glioma.

Of particular interest is case 3, in which a patient who survived a brain-stem glioma at the age of 1 year with radiation therapy, later developed a clinically significant meningioma at the age of 25 years. Also of interest is case 4, a malignant meningioma of the sphenoid ridge contiguous to a granular cell tumor of the posterior pituitary gland, diagnosed at necropsy.

COMMENT

Meningioma and Breast Cancer

Whereas case reports of separate tumors occurring in combination are frequent, it is difficult to know whether these occurrences are random events or, alternatively,

Table 4.—Meningioma and Other Primary Brain Tumors

Patient No./ Sex/Age,* y	Type of Meningioma	Type of Additional Tumor	Comment
1/F/56 (56)	Parietal convexity meningioma	Ependymoma	. . .
2/F/60 (60)	Parasagittal meningioma	Glioblastoma	. . .
3/F/25 (1)	Petrous ridge meningioma	Brain-stem glioma at age 1 year	Received radiation for glioma
4/M/73 (73)	Sphenoid ridge malignant meningioma	Posterior pituitary tumor	Incidental meningioma noted at necropsy
5/F/69 (65)	Unknown site meningioma	Pituitary adenoma	. . .
6/M/83 (83)	Frontal meningioma	Glioblastoma multiforme	Incidental meningioma noted at necropsy

*Age at diagnosis of meningioma and, parenthetically, age at diagnosis of other brain tumor.

represent a unique association among the tumors.[7] Our data do not clearly support a relationship between meningiomas and breast cancers.

An association between meningiomas and breast cancers has been postulated on the basis of epidemiologic, clinical, and physiologic data. Meningiomas occur more commonly in women; in our series, 63% of the patients were women. In certain sites, meningiomas have an even stronger gender association. Sphenoid ridge meningiomas en plaque occur almost exclusively in women, and 80% of spinal canal meningiomas occur in women.[8] Previously, we[9] described a predilection for multiple primary tumors of the breast and female genital tract, which occurs only in those patients with meningioma who have sphenoid ridge meningiomas.

The presence of progesterone and other sex steroid receptors on meningiomas[10] has sparked widespread research interest; it also provides a physiologic analogy to breast cancer and a theoretical explanation for epidemiologic data showing a preponderance of meningiomas in female individuals.

Our review of the literature shows that, despite the publication of several case reports, only four studies have examined the relationship between meningiomas and breast cancers by means of statistical methods. Schoenberg et al[4] studied all cases of multiple primary tumors that were found through a Connecticut population-based tumor registry. Of 130 cases in which at least one of the tumors involved the nervous system, eight were the combination of breast cancer and meningioma for which the authors found that $P<.05$.

Helseth et al[11] examined the Norwegian Cancer Registry and found that of patients registered with breast cancer, 21 later developed a meningioma, compared with an expected 11 cases. The authors state that this ratio is significant. They also found an increased risk of developing breast cancer in patients with meningiomas who were 50 to 64 years old ($P=.042$).

Bellur et al[12] studied 76 meningioma cases and found a significantly increased incidence of extraneural malignancies. In contrast to the findings of Schoenberg et al[4] and Helseth et al,[11] their report included only one patient who had breast cancer. Adami et al[13] examined a series of patients with breast cancer and found that 41 had intracranial tumors, including 15 who had meningiomas. However, 10 of the 15 meningiomas were diagnosed only at autopsy and were deemed clinically insignificant. Adami et al concluded that the incidence of clinically important intracranial lesions in patients with breast cancer was lower than expected.

Thus, our study does not support the findings of Schoenberg et al.[4] The differences between our findings and those of Schoenberg et al may be explained by the marginal significance of the association between breast cancer and meningioma. Schoenberg and colleagues based their conclusions on a small number of cases (eight) and comparisons of many tumor combinations, and they found one case for which $P<.05$. Conversely, had we observed two additional cases of breast cancer in our patients with meningioma, making a total of 14 cases, our SMR of 2.06 would have fallen within the 95% confidence limits (1.15 to 3.53), indicating a significant association.

It is possible that meningiomas are heterogeneous and that subpopulations exist in which a relationship between meningioma and breast cancer does exist. If, for example, sphenoid ridge meningiomas were exceptional, their effects might be blunted statistically since 85% of meningiomas arise from other intracranial locations.[9]

Meningioma and Other Primary Neoplasms

We observed an increased number of additional nonmeningeal primary brain tumors. The additional primary brain tumors found in our sample were of diverse histologic type.

There are intriguing theoretical explanations regarding an association between brain tumors of different types. First, Deen and Laws[14] described a series of 18 patients with multiple primary brain tumors, but they did not compare their findings against any reference population. They suggested that in the case of contiguous tumors the "irritative" effect of the first tumor may contribute to the development of the second tumor. Second, other possibilities include unrecognized genetic factors, such as undiagnosed phakomatoses, accounting for the multiplicity of types of brain tumors. Third, some authors[15,16] have suggested that prior irradiation predisposes to meningiomas. If true, then irradiation for a first tumor could account for the meningiomas that occur subsequently. In our series, one patient developed a meningioma 24 years after irradiation for a childhood glioma. Last, a detection bias may exist; a patient with one brain tumor may be more likely to have a second one detected because the physicians may evaluate the same complaints differently in patients who have had a previous brain neoplasm than in those who have not had one.

The finding of an increased number of thyroid cancers in our meningioma population was unexpected. Interestingly, Helseth et al[11] also found an increased number of thyroid cancers in their meningioma population. However, in their analysis of a relatively small number of patients, they minimized the statistical significance of that finding.

Although the occurrence of tumors of the central nervous system in women and thyroid cancers in all patients reached significance, the data may be misleading. This is because of the problem of "multiple comparisons," in which, if enough comparisons are made, something will falsely appear to be significant. In our series, we made 25 total comparisons (Tables 1 through 3) and found significance in two, each based on a small number of cases (four central nervous system tumors in women and three thyroid cancers).

In conclusion, breast cancer does not appear to occur more frequently in patients with meningioma when all meningiomas are considered together, regardless of site of origin. The possible positive association of meningiomas with other primary brain tumors and thyroid cancer is notable, but is by no means conclusive.

Statistical review was provided by Michael J. McFarlane, MD, Case Western Reserve University, Cleveland, Ohio.

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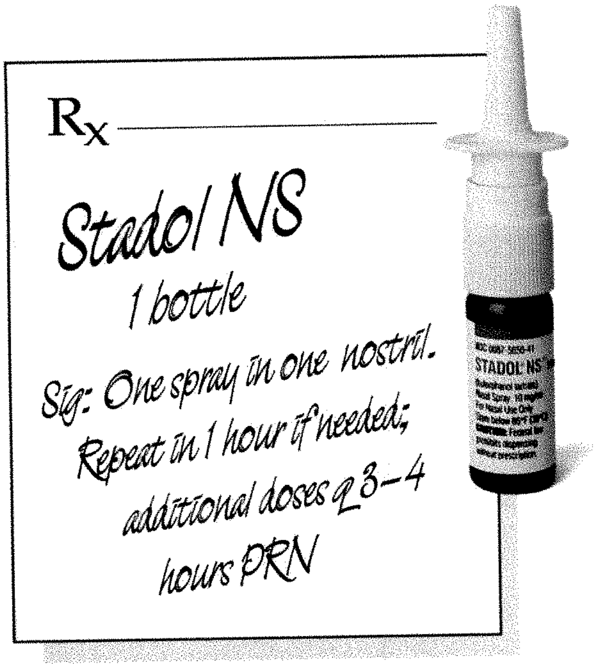

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Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

PRECAUTIONS
Head Injury and Increased Intracranial Pressure
As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control
Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease
In patients with severe hepatic or renal disease the initial dosage interval for STADOL NS should be increased to 6-8 hours until the response has been well characterized. Subsequent doses should be determined by patient response rather than being scheduled at fixed intervals.

Cardiovascular Effects
Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Drug Interactions
Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (cimetidine, erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

The fraction of STADOL NS absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if STADOL NS is administered concomitantly with, or immediately following, a nasal vasoconstrictor.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Use in Ambulatory Patients
Drowsiness and dizziness related to the use of butorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc.). Patients should be told to use caution in such activities until their individual responses to butorphanol have been well characterized.

Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects.

Patients should be instructed on the proper use of STADOL NS.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of butorphanol has not been adequately evaluated.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/sq.m.) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/sq.m.) subcutaneous dose.

Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation.

Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. Pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/sq.m.) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (5.1 mg/sq.m.) and 60 mg/kg/oral (10.2 mg/sq.m.) also showed higher incidences of post implantation loss in rabbits.

Labor and Delivery
STADOL NS is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

Nursing Mothers
Butorphanol has been detected in milk following administration of STADOL Injectable to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 microgram/liter of milk in a mother receiving 2 mg IM four times a day).

Although there is no clinical experience with the use of STADOL NS in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

Pediatric Use
Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use
Initially a 1 mg dose of STADOL NS should generally be used in geriatric patients and 90-120 minutes should elapse before deciding whether a second 1 mg dose is needed.

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65. Elderly patients may be more sensitive to its side effects. Results from a long-term clinical safety trial suggest that elderly patients may be less tolerant of dizziness due to STADOL NS than younger patients.

ADVERSE REACTIONS
A total of 2446 patients were studied in butorphanol clinical trials. Approximately half received STADOL Injectable with the remainder receiving STADOL NS. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short- and long-term clinical trials in patients receiving butorphanol by any route and from post-marketing experience with STADOL Injectable. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo treated patients in controlled trials.

REACTIONS
The most frequently reported adverse experiences across all clinical trials with STADOL Injectable and STADOL NS were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with STADOL NS only, nasal congestion (13%) and insomnia (11%) were frequently reported.

The following adverse experiences were reported at a frequency of 1% or greater, and were considered to be probably related to the use of butorphanol:

BODY AS A WHOLE: asthenia/lethargy*, headache*, sensation of heat

CARDIOVASCULAR: VASODILATION*, PALPITATIONS

DIGESTIVE: ANOREXIA*, CONSTIPATION*, dry mouth*, nausea and/or vomiting (13%), stomach pain

NERVOUS: anxiety, confusion*, dizziness (19%), euphoria, floating feeling, INSOMNIA (11%), nervousness, paresthesia, somnolence (43%), TREMOR

RESPIRATORY: BRONCHITIS, COUGH, DYSPNEA*, EPISTAXIS*, NASAL CONGESTION (13%), NASAL IRRITATION*, PHARYNGITIS*, RHINITIS*, SINUS CONGESTION*, SINUSITIS, UPPER RESPIRATORY INFECTION*

SKIN AND APPENDAGES: sweating/clammy*, pruritus

SPECIAL SENSES: blurred vision, EAR PAIN, TINNITUS*, UNPLEASANT TASTE* (also seen in short-term trials with STADOL® NS™ [butorphanol tartrate] Nasal Spray)

(Reactions occurring with a frequency of 3-9% are marked with an asterisk.* Reactions reported predominantly from long-term trials with STADOL NS are CAPITALIZED.)

The following adverse experiences were reported with a frequency of less than 1%, in clinical trials or from post-marketing experience and were considered to be probably related to the use of butorphanol.

CARDIOVASCULAR: hypotension

NERVOUS: abnormal dreams, agitation, *drug dependence*, dysphoria, hallucinations, hostility

SKIN AND APPENDAGES: rash/hives

UROGENITAL: impaired urination

(Reactions reported only from post-marketing experience are *italicized.*)

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term STADOL NS trials and from post-marketing experiences under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

BODY AS A WHOLE: edema

CARDIOVASCULAR: hypertension

NERVOUS: *convulsion, delusions*, depression

RESPIRATORY: *apnea*, shallow breathing

(Reactions reported only from post-marketing experience are *italicized.*)

DRUG ABUSE AND DEPENDENCE
Although the mixed agonist-antagonist opioid analgesics, as a class, have lower abuse potential than morphine, all such drugs can be and have been reported to be abused.

Chronic use of STADOL Injectable has been reported to result in mild withdrawal syndromes, and reports of overuse and self-reported addiction have been received.

Among 161 patients who used STADOL NS for 2 months or longer approximately 3% had behavioral symptoms suggestive of possible abuse. Approximately 1% of these patients reported significant overuse. Symptoms such as anxiety, agitation, and diarrhea were observed. Symptoms suggestive of opioid withdrawal occurred in 2 patients who stopped the drug abruptly after using 16 mg a day or more for longer than 3 months.

Special care should be exercised in administering butorphanol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is necessary, such patients should be closely supervised.

OVERDOSAGE
Clinical Manifestations
The clinical manifestations of overdose are those of opioid drugs, the most serious of which are hypoventilation, cardiovascular insufficiency and/or coma.

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment
The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

DOSAGE AND ADMINISTRATION
Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, patients with hepatic or renal disease or in labor requires extra caution (see PRECAUTIONS). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60-90 minutes, an additional 1 mg dose may be given.

The initial two dose sequence outlined above may be repeated in 3-4 hours as needed.

Depending on the severity of the pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients single additional 2 mg doses should not be given for 3-4 hours.

Safety and Handling
STADOL NS is an open delivery system with increased risk of exposure to health care workers.

In the priming process, a certain amount of butorphanol may be aerosolized, therefore the pump sprayer should be aimed away from the patient or other people or animals.

The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED
STADOL NS is supplied in a child-resistant prescription vial containing a metered-dose spray pump and protective clip with dust cover, a bottle of nasal spray solution, and a patient instruction leaflet. On average, one bottle will deliver 14-15 doses if no repriming is necessary.

NDC 0087-5650-41: 10 mg per mL, 2.5-mL bottle.

Storage Conditions
Store below 86°F (30°C). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CAUTION: Federal law prohibits dispensing without prescription.

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The **Annual Meeting** of the Society will be held September 18-20 at the Fairmont Hotel in San Francisco. The program will include Symposia on: **Recovery of Function Following Injury To Essential Cortical Areas, Intraoperative Neurophysiological Monitoring, Digital EEG: What It Does and What We Would Like It To Do**, as well as Scientific Sessions, posters, and a technical exhibit.

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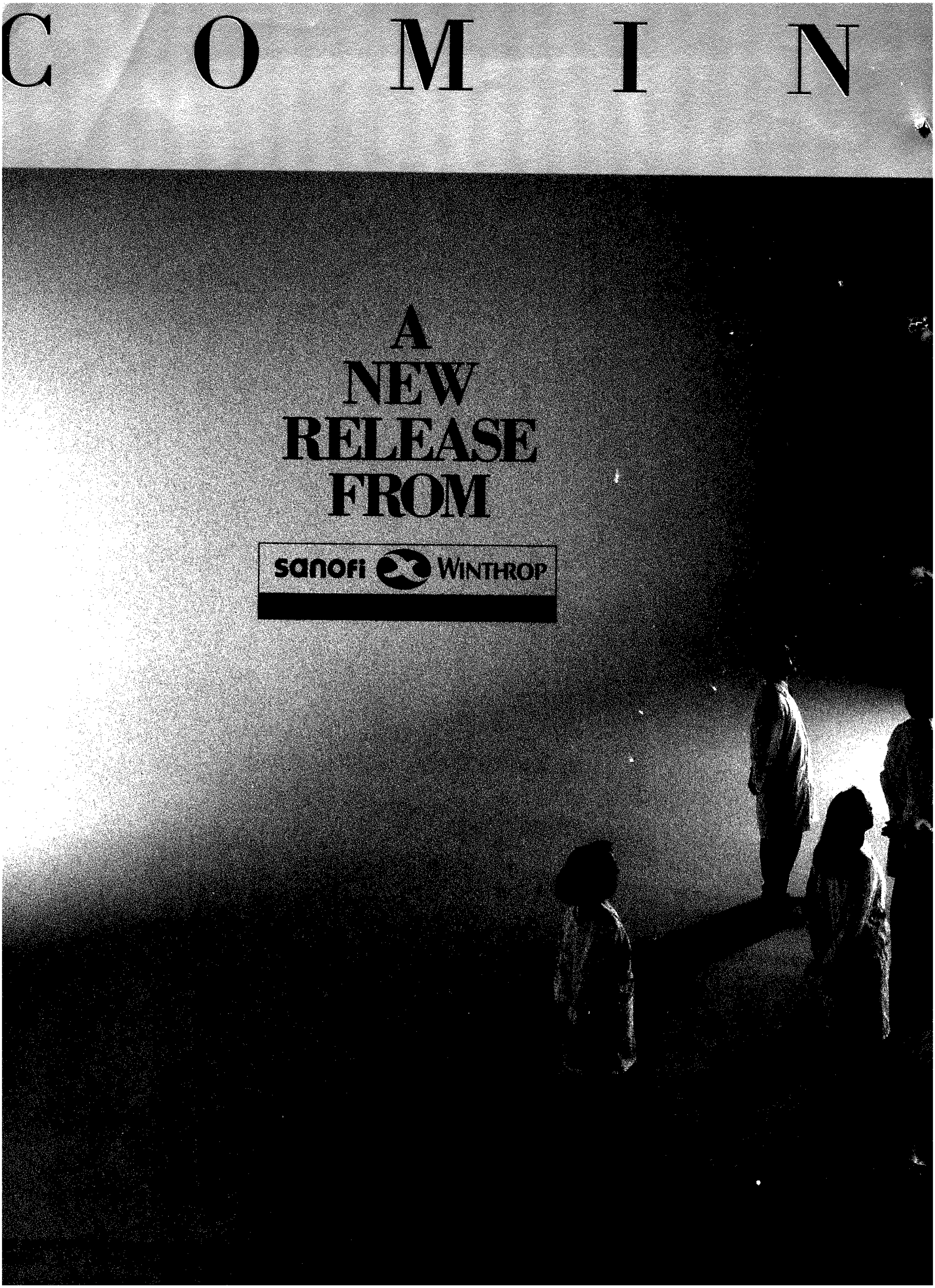
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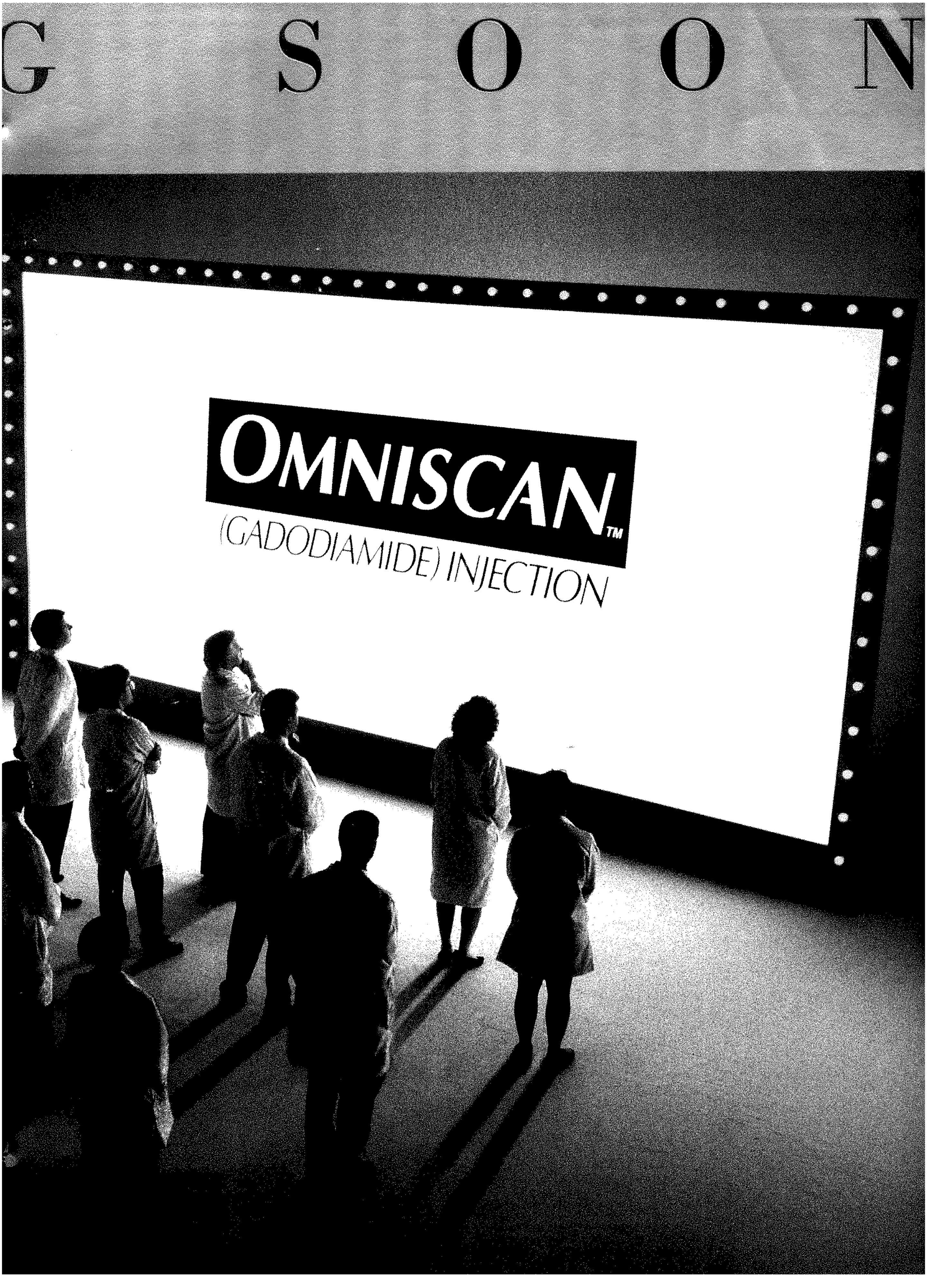
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Developmental Consequences of Childhood Frontal Lobe Damage

Paul J. Eslinger, PhD; Lynn M. Grattan, PhD; Hanna Damasio, MD; Antonio R. Damasio, MD, PhD

• A 33-year-old woman underwent neurologic and neuropsychological studies 26 years after she sustained damage to the frontal lobe. The findings of the neurologic examination were normal, and magnetic resonance imaging revealed a lesion in left prefrontal cortex and deep white matter. Cerebral blood flow studies showed an abnormal pattern in both left and right frontal regions. The patient exhibited striking neuropsychological defects in higher cognition, most notably in self-regulation of emotion and affect and in social behavior. Analysis of her behavioral development failed to yield a pattern of abrupt onset of defect immediately after the lesion occurred. On the contrary, there was a *delayed onset* of defects, followed by a period of seeming *progression*, and finally an *arrest* of development in adolescence. We suggest that this peculiar pattern is the natural consequence of the varied changes that occurred in brain development and social cognition during the patient's formative years. While certain long-term neuropsychological deficits in our case are similar to those following frontal damage in adults, the delayed onset and progression of deficits are different.

(*Arch Neurol.* 1992;49:764-769)

The neuropsychological consequences of frontal lobe lesions in adults have been described in detailed case studies and group analyses.[1-13] The spectrum of associated cognitive and behavioral changes have been incorporated in several models that address not only location of lesion and disruption of intrinsic frontal lobe mechanisms, but also pathologic features within the multiple neural systems that interact with the frontal lobes.[13-16] By comparison, few cases of focal, stable frontal lobe lesions sustained in childhood have received comparable attention. Those available allude to significant, long-term impairment in social behavior and emotional maturity.[17-21] Study of such cases is relevant to diagnostic, management, and theoretical issues, many of which have been raised only through investigations with animal models or through developmental studies in normal children.[22-31]

Neuropsychological impairments associated with childhood cerebral diseases have been noted to continue well beyond the recovery of overt physical and neurologic symptoms. Unlike the effects of adult brain injury, the neuropsychological consequences of early cerebral injury may not be immediately apparent or may vary throughout development.[32-34] In a comparative study 30 years ago of children and adults with brain lesions, Teuber and Rudel[35] differentiated three patterns of outcome after childhood lesion: (1) fixed impairments with no recovery over time; (2) recovery over time by various compensatory processes; and (3) delayed onset of impairments throughout development. More recent neuropsychological studies indicate that there may be some anatomic basis for these outcome differences. That is, nonfrontal cerebral lesions in childhood have been associated with impairments that are frequently identifiable in the early stages and show various degrees of recovery, such as aphasia, amnesia, and visual disorders.[36-39] However, frontal lobe damage in childhood poses special questions about the pattern of outcome that may arise from the fact that the frontal lobes undergo a longer, multistage maturation process extending well into adolescence.[13,26-30,40-42] Hence, frontal lobe damage at varying ages prior to adulthood may lead to a different onset of impairments and pattern of recovery.

In the following study, we examined the consequences of early frontal lobe damage on higher cognitive and psychological development in a 33-year-old woman who sustained her injury at 7 years of age.

METHODS

Neuropsychological Studies

The patient underwent comprehensive neuropsychological and neuroimaging studies 26 years after she sustained damage to the frontal lobe. Cognitive evaluation with the Benton Laboratory Comprehensive Neuropsychological Examination assessed intellect, learning and memory, language, visual perception, constructional praxis, executive functions, and academic achievement.[9,43-52]

The patient's personality and social behavior were assessed through numerous clinical interviews, the Minnesota Multiphasic Personality Inventory, Hogan's Empathy Scale,[53] and a Moral Judgment Interview.[54] Collateral data were obtained through the patient's daily diary, her parents' report, academic records, and notes from psychotherapy sessions spanning 7 years of young adulthood.

Neuroimaging Studies

Neuroimaging studies included computed tomography, magnetic resonance imaging (T_1- and T_2-weighted images), and single photon emission computed tomography with xenon 144. These images were analyzed by an investigator blinded to the patient's neurologic and neuropsychological data. A standard method of anatomical analysis was used to interpret all abnormal images.[55]

RESULTS

Premorbid History

The patient was the older of two children born to the same pair of biological parents in a middle-class semirural community. Her birth was uncomplicated and followed a normal pregnancy. Developmental milestones (eg, speech, language, sitting up, and toilet training) were entirely nor-

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Reprint requests to Division of Neurology, The Milton S. Hershey Medical Center, 500 University Dr, Hershey, PA 17033 (Dr Eslinger).

mal. Social and emotional development were appropriate until the time of her brain injury at 7 years of age. Her first-grade teacher noted her to be always proper, immaculately dressed and groomed, and often the only child in the classroom to remember her umbrella on rainy days. Premorbidly, the patient's level of academic achievement was average. Her parents and sister are also of average educational and occupational achievement. There is no family history of mental illness, substance abuse, or social-emotional impairment.

Neurologic History

At 7 years of age, the patient sustained a spontaneous intraparenchymal hemorrhage of unknown cause in the left frontal region. An emergency craniotomy was performed to evacuate the hemorrhage. The patient remained in coma for 5 days and was hospitalized for 1 month. Thereafter, with the exception of treatment for primary generalized tonic-clonic seizures, which have been well controlled, her physical recovery was complete and normal. The parents were instructed to return the child to school and usual activities. Clinical neurologic examination results have been normal.

Neuropsychological Examination

The patient's clinical presentation varied with the context of evaluation. Within her familiar home environment, she was friendly, verbal, and well oriented. During examination at the University of Iowa Hospitals and Clinics, Iowa City, she was hostile, with puerile affect and disinhibition. A consistent pattern during personality and cognitive assessment was her lack of attention to detail, her disorganized approach to problem solving, her difficulty in establishing a plan and in executing multiple steps toward a relatively remote goal, and cognitive rigidity. She demonstrated an impulsive response style and, unless encouraged, failed to give in-depth thought to questions and tasks.

Results of formal testing indicated an overall low-average range of intellect (Wechsler Adult Intelligence Scale-Revised intelligence quotient [IQ] scores: verbal IQ, 81, performance IQ, 84, and full scale IQ, 80). Considerable subtest variability occurred. The patient had particular difficulty with subtests requiring "freedom from distractibility" (ie, arithmetic, digit span, and digit symbol substitution), but was average in verbal and nonverbal reasoning, comprehension, and perceptual ability. Despite her 12 years of formal education, her academic achievement levels were at the third-grade level or lower in spelling, arithmetic, and oral word reading. Her learning and memory were within the low-average range, and she did not appear amnesic in any way.

Her conversational speech was spontaneous, fluent, and nonparaphasic, without evidence of word selection or prosodical disturbance. Dichotic listening revealed a mild left ear extinction, with normal results on screening audiometry. Her verbal associative fluency was defective, but her category (semantic) fluency was intact.

Visual pattern discrimination, spatial judgment, and block constructions were within the average range. Copy of the Rey-Osterrieth complex figure was spatially disorganized, perseverative, and sloppy. Her construction improved significantly, however, when it followed a programmed format that presented one element at a time.[56]

Measures of executive and self-regulatory processes indicated significant difficulties in organizing information, utilizing examiner feedback to modify her responses, and planning toward a remote goal. She exhibited significant cognitive rigidity in tasks requiring shifting of response set[51] (ie, reactive flexibility) and divergent production[49] (ie, spontaneous flexibility). Finally, on a modified cognitive estimation task,[9] she had difficulty in making judgments about environmental events. For instance, she reported that 90% of the US population was male; proposed that one could drive from New York to Los Angeles in 6 hours; and decided that race horses galloped at a rate of 5 miles per hour.

Personality and Social Behavior

The patient presented an austere but sloppy appearance. Her clothing consisted of a simple dress and sandals, without makeup. She specifically pointed out that her attire, hairstyle, and omission of makeup were purposely selected to be compatible with the teachings of her religion. However, since our evaluation marked a special occasion, she decided to make an exception and wore a necklace.

Assessment of the patient's personality and social and emotional development suggested that she had significant difficulties with managing and expressing strong emotions, establishing meaningful relationships, and integrating multiple aspects of her social and emotional self into a stable and consistent presentation over time. Specifically, the Minnesota Multiphasic Personality Inventory profile was valid, but abnormal (Welsh code 46″98′71230-5: F′LK/). Women generating a similar pattern of responses have been described as excessively demanding and dependent, unable to profit from experience, and harboring considerable hostility, which they are unable to effectively or directly express. In addition, the patient's responses were similar to those of individuals who experience and demonstrate significant emotional shallowness toward others and have seriously disrupted interpersonal relationships. She also generated a very low score on the standardized measure of empathy (27:2 SD below the mean), which was confirmed by parental report on an equivalent form. The finding indicates that the patient has unusual difficulty in apprehending the viewpoints and situations of other people.

Her analysis of moral dilemmas suggests that she views such complex situations in terms of concrete and stereotypic notions of "good" and "bad" behavior. In the forefront of her responses are fixed rules. For instance, she decided it would be wrong for a poor young man to steal an expensive drug from a greedy dispenser because, "It's against the law. It's against the Ten Commandments. That's against the Bible. That's against morals." When the genuine plight of the poor young man was pointed out to her, she quickly changed her approach to the problem. She indicated that when laws and rules do not permit a person to do what they want, then the person should change the rules, basing her response on motives of instrumental hedonism and interpersonal concordance. The discrepancy between her responses was never resolved. Her approach to these conflicting situations did not adhere to a set of consistent ethical principles or values, but was driven by a varying rationale that would serve to meet immediate needs or to indicate in an absolute inflexible way what was good and bad behavior. Her level of moral reasoning most closely resembled that of early adolescents, 10 to 13 years of age.[54]

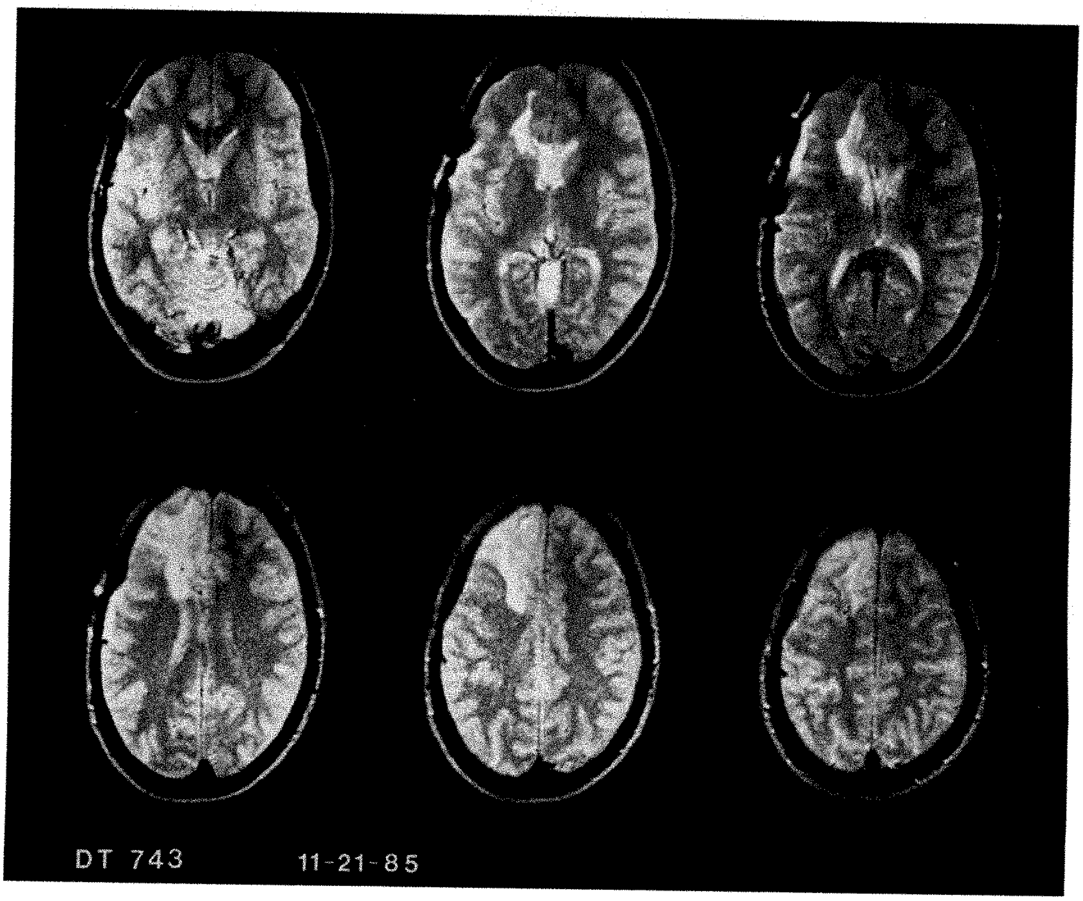

Fig 1.—*Magnetic resonance imaging scan (T_2-weighted images) showing deep left prefrontal lobe lesion.*

Through retrospective analysis of family and academic records, as well as extensive interviews with the patient's parents, we attempted to gauge the impact of her early frontal lobe lesion on her daily living. During the 3 years immediately following her injury (7 to 10 years of age), she became a slower learner and a lower achiever in school. In late childhood and early adolescence, significant difficulties became progressively evident in social and emotional domains. She eventually maintained only one friend, alienating herself from others through noncooperative interactions and frequent arguments. She became pregnant 1 year after high school graduation by the first man she dated, and was married. After 7 years of marital conflicts, her husband divorced her and gained custody of their child because of the patient's impulsive and immature behavior. She appeared unable to regulate her emotions and unable to learn from her experience as a wife, homemaker, and mother. For instance, while she was able to wipe a table, wash a dish, measure a quantity, and open a can, she could not plan or execute the steps necessary for meal preparation or even cleaning a room. Thereafter, her promiscuity increased. She proclaimed her love for numerous antisocial and unsavory characters, reporting up to seven boyfriends at a time. She eventually met a self-proclaimed preacher, and after a 2-month courtship decided to marry him because his religion accepted second marriages. This relationship, however, has been marked by conflicts and abnormal sexual activity for several years. She justifies her difficult relationship as "obedience to her religion" and cites skewed and concrete biblical references to justify it. Meanwhile, her increasing church involvement appears to provide a structure for her identity and behavior, dictating her dress, interpersonal contacts, and daily activities. Her few friendships are initiated through the church, but are short-lived after repeated overstepping of interpersonal boundaries. She extends her visits beyond the time for which she is welcome and quickly depends on newfound friends to meet all of her emotional needs.

The patient's vocational record has also been maladaptive. After high school graduation she attended beautician training school for 1 year. However, she was dismissed from her first position because she persistently made hurtful statements, asked embarrassing questions, and gave impulsive responses. Since that time she has been unable to hold a job for more than a few weeks, although she has the intellectual capacity and physical ability to learn the basic tasks of a semiskilled occupation. Her work is characterized by poor interpersonal skills, by her inability to execute the required activities throughout the course of a day, and by her failure to learn from mistakes. Moreover, she responds to criticism by externalizing blame, becoming obstinate, and telling her employers how they should be managing their business. Despite a poor work record for 12 years, the patient remains rigid in her job-hunting strategies, naive, and unrealistic about her vocational abilities. Her approach is to read the newspaper and apply for positions that "look interesting,"

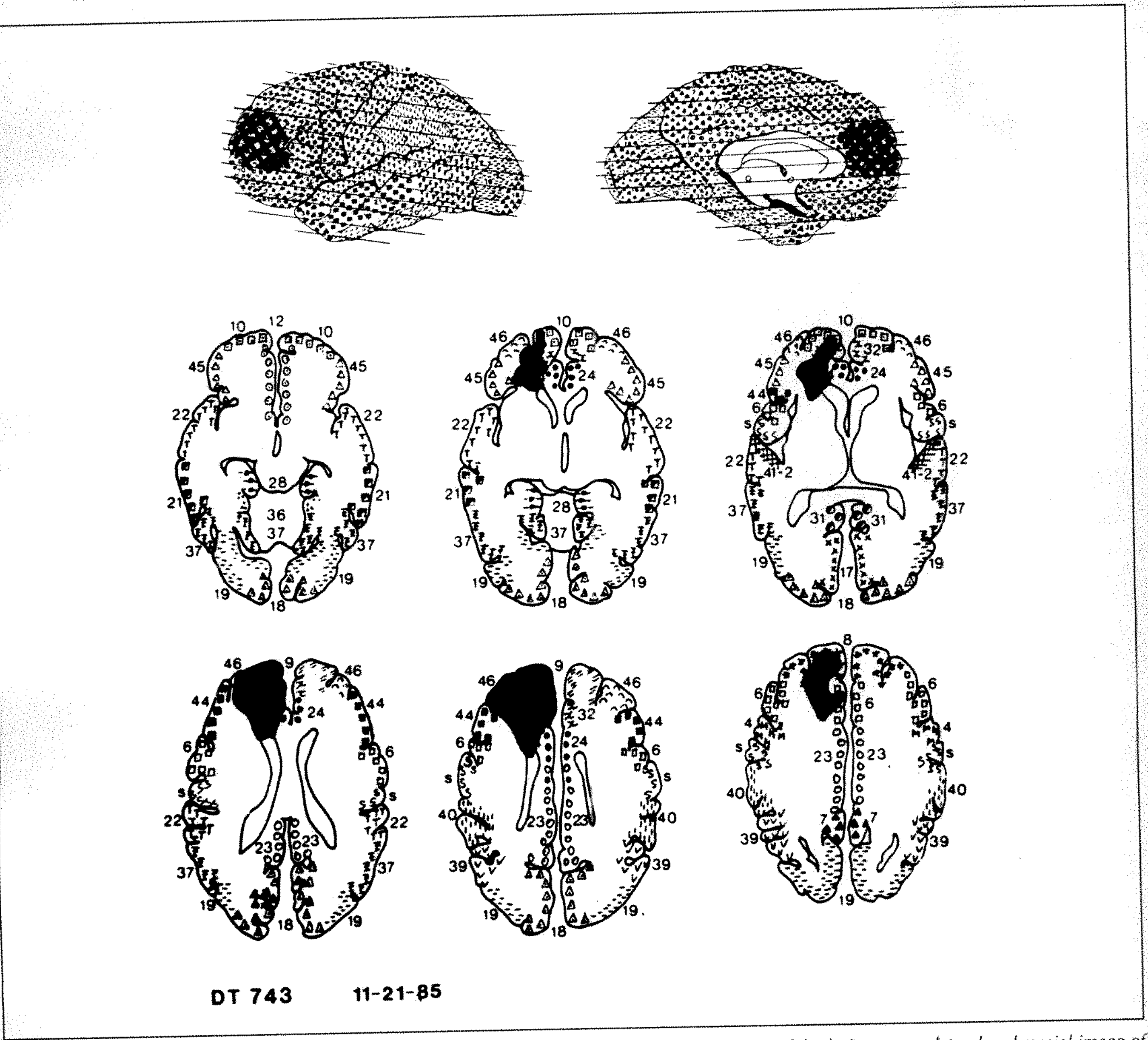

Fig 2.—*Depiction of the lesion seen in Fig 1 on the best-fitting template system and the projection of the lesion onto a lateral and mesial image of the left hemisphere.*

such as an airline stewardess and a store manager. Another aspiration is to open a religious book store in the West, because a friend informed her there were none. When asked about these vocational goals, her responses are devoid of any financial or practical planning, as well as anticipation of the various steps leading to employment.

Neuroimaging Results

Neuroanatomical interpretation of the magnetic resonance images revealed damage in the left prefrontal region, involving Brodmann's areas 9, 46, and 32. The lesion extended deep into the white matter, reaching the most superior portion of the left frontal horn and damaging the white matter underlying Brodmann's areas 45 and 24. No structural abnormality could be detected in the right frontal lobe (Figs 1 and 2).

Single photon emission computed tomography with xenon 144 inhalation revealed abnormally low blood flow in both left and right frontal cortices, suggesting bilateral abnormal function (Fig 3).

COMMENT

The patient's frontal lobe lesion at 7 years of age occurred during an important phase of maturation.[13,26-28,30,40-42,57-60] Neurobiological events such as myelination, elaboration of dendritic features in prefrontal pyramidal neurons, and corticocortical connectivity, which are prolonged postnatal processes, remain incomplete at this age. Development of frontal lobe cognitive operations are far from adult and even adolescent levels. The results documented in this study indicate that maturation of systems dependent on frontal cortex was inexorably altered by the childhood lesion, severely interfering with development of adaptive behavior at subsequent stages of the patient's life. The consequences have continued to be expressed over a long period in cognitive and social domains,

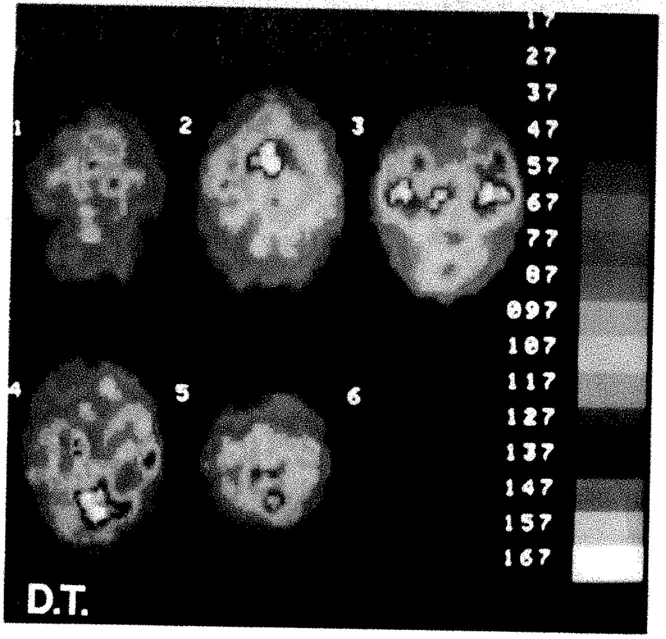

Fig 3.—*Single photon emission computed tomographic study with xenon 144 inhalation showing low flow in the left and right frontal regions.*

though in a pattern that is quite different from that observed in adults. The most disabling consequences were not the most immediate. The patient's initial difficulties were registered in terms of a slower rate of academic learning. During early adolescence, 3 to 5 years after the lesion occurred, social impairment became increasingly evident. The patient's adjustment appeared to decline gradually as she encountered progressively more complex social situations. At the same time, developmental psychological demands were escalating with tasks such as identity formation, adoption of sexual attitudes, internalization of social and moral values, exploration of occupational roles, and participation in meaningful interpersonal relationships. We believe that the appearance of progressive impairment resulted from an increasing discrepancy between the burgeoning demands of adolescent development and altered maturation of frontal lobe neural and cognitive systems. According to available indexes, the patient's social and psychological development was virtually arrested in early adolescence. As an adult, the patient shows many behavioral and cognitive deficits that are similar to those observed in cases of adult-onset frontal lobe damage. These include a persistent pattern of deficient decision making, hallmarked by capricious social and vocational judgment, rigidity, impulsivity, interpersonal conflict, and little ability to synthesize the lessons of experience. These deficits, which are not accountable by measurable impairment of perception, memory, language, and reasoning, have had a pervasive effect on the patient's life, precluding any consistent form of productive, goal-directed behavior.

This unusual course of impairment may be related to alteration of cognitive and neurobiological events. On a cognitive level, the patient failed to acquire the executive and self-regulatory processes associated with the frontal lobe. This became most apparent in early adolescence, several years after her lesion occurred, at a time when maturation of such processes is critical to psychological development, a pattern that bears certain similarities to the primate model.[61] Identity formation, for example, requires impulse control, synthesis of personal and social experiences across time and space, and integration with other forms of knowledge. Another higher cognitive process such as considering a wide range of possibilities, associated consequences, and alternative viewpoints (ie, cognitive flexibility) partly underlies development of moral maturity and empathy. We recently reported that there is a significant correlation between measures of cognitive flexibility and empathy in adult patients who have suffered brain damage.[62] Furthermore, this interrelationship was most pronounced after injury to the left frontal region,[63] where our patient sustained an early lesion. In summary, we propose that the early frontal lobe lesion in this patient had a strong impact on her social and psychological maturation by altering underlying cognitive processes.

At the neurobiological level, there are diverse anatomical and physiological processes that may have been affected by the patient's lesion and may have influenced her course of impairment. Early frontal lobe ablation has been associated with subsequent anatomical changes in proximal and distal brain areas.[64,65] In the nonhuman primate, these take the form of anomalous gyri and sulci in the frontal lobe as well as in cortical areas interconnected with that site. With early *unilateral* frontal lobe ablation, these anatomical changes are observed in the contralateral frontal lobe as well. This may be the reason why our patient's clinical history and neuropsychological results are so similar to those in cases with bilateral lesions.[17-21] It is also likely that the bilateral cerebral blood flow changes in the frontal regions reflect this contralateral effect.

Analysis of electroencephalographic phase and coherence in normal children has indicated that discrete "growth spurts" occur in each frontal lobe throughout childhood and adolescence.[42] These correspond well to Piaget's cognitive-development stages. Our patient's lesion occurred at an age that would have certainly impeded such physiological maturation. But the time frame in which deficits become clinically evident may depend on the precise site of lesion within the frontal lobe and the role of that site in subsequent maturation. In our patient, the lesion was well restricted to the polar and mesial portion of the left prefrontal cortex and deep white matter, and her defect did not become apparent until early adolescence, 3 to 5 years after the lesion occurred.

Another important facet of altered neurophysiological processing, particularly as it pertains to the patient's social impairment, may involve the autonomic nervous system. Recently, Damasio et al[15] have shown that adults with frontal lobe lesions and acquired social conduct defects exhibit a selective deficiency in autonomic responsiveness to socially meaningful stimuli. They have hypothesized that the failure to evoke autonomic responses under these conditions indicates an inability to activate "somatic states" that have been learned previously in association with social situations and that play a key role in decision making. This process would appear to be pertinent to social development and learning to recognize, control, and properly associate a variety of somatic states with social situations and their consequences. The patient may never have acquired those associations and thus may be unable to evoke in any form the expected somatic states to guide her social behavior. However, this remains a hypothesis to be tested in cases of early frontal lobe lesion.

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Original Contribution

Asymmetric Cortical Degeneration Syndromes

A Proposed Clinical Classification

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• Twenty-six patients presented with slowly progressive focal neurologic symptoms that conformed clinically to one of three categories: aphasia, perceptuomotor dysfunction, or neuropsychiatric dysfunction. Of 12 patients with progressive aphasia, seven were dysfluent and five were fluent. Nine patients had progressive perceptuomotor impairment due to bilateral parietal lobe atrophy, which also included frontal lobe signs in seven patients and occipital lobe signs in three patients. The right hemisphere was more severely involved in five patients and the left hemisphere in four. Five patients had a progressive neuropsychiatric syndrome, and there was also generalized spasticity in three patients due to frontal lobe atrophy. The clinically suspected anatomic localization of cortical atrophy or hypoperfusion in all three categories was confirmed with neuroimaging techniques. A brain biopsy specimen from one patient showed mild, nonspecific degenerative changes. A clinical classification scheme incorporating our observations as well as the observations of others is presented to aid in the recognition of these syndromes.

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Progressive focal neurologic deficits can result from a relatively circumscribed degenerative process, as Pick[1] emphasized in his original report on a patient with progressive aphasia and dementia due to asymmetric atrophy of the left temporal lobe. Since then, other clinical permutations of focal cerebral degenerative processes have been described, including isolated progressive aphasia without dementia,[2] progressive frontal lobe syndromes,[3-5] progressive apraxia,[6] progressive parietal lobe syndromes,[7,8] and progressive prosopagnosia.[9] The neuropathologic substrates, which differ among patients, include increased neuronal lipofuscin,[2,10] severe gliosis,[8] spongiform atrophy,[11] Pick's disease,[12] Alzheimer's disease,[13,14] and an unusual combination of pathologic features.[15] Corticobasal ganglionic degeneration with neuronal achromasia produces relatively focal parietofrontal atrophy and changes in certain subcortical nuclei (most consistently, the substantia nigra).[16-18] However, neuronal achromasia has also been associated with progressive aphasia.[19] Motor neuron disease is occasionally accompanied by clinically distinctive dementia syndromes, including frontal lobe features[20] and progressive aphasia.[21]

Different clinical disorders do not appear to have distinctive histopathologic features; thus, clinical symptoms may be determined solely by the neuroanatomic location of the degenerative process.[10] This point is of diagnostic importance because modern neuroimaging techniques can reveal focal areas of atrophy and help to distinguish focal cerebral degenerative processes from one another and from clinically typical cases of Alzheimer's disease.

Despite increasing clinical awareness in the last decade about focal cerebral degenerative diseases, they remain underrecognized. In part, this is the result of uncertainty about nosologic relationships between the variously described pathologic entities underlying these conditions. It also reflects an inveterate, but imprecise, tendency to regard dementia as a "diffuse" cognitive disturbance,[22,23] implying a certain pathophysiologic and clinical homogeneity among patients with different dementing illnesses. Hence, patients with unusual cognitive asymmetries and who perform imperfectly in cognitively disparate areas are considered to have a "diffuse" disturbance, which, by inference, is generally equated with Alzheimer's disease. This is true in some instances.[24] However, it has been shown that appreciation of the sometimes subtle clinical distinctions between typical Alzheimer's disease and other forms of dementia in patients with a clinical diagnosis of "diffuse dementia" or Alzheimer's disease may occasionally lead to an alternative diagnosis and even occasional recognition of a treatable condition.[25,26] Because there is unequivocal evidence that some patients with relatively focal degenerative syndromes have more diffuse clinical and pathologic abnormalities, we use the term *asymmetric cerebral degeneration syndrome* (ACDS) to refer to patients whose clinical condition is dominated by a focal syndrome but whose neuropsychologic profile may reveal disproportionately milder impairment in other cognitive domains.

Increased clinical recognition of ACDS is an important early step in further elucidating the nosologic relationships

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Table 1.—Demographics of 26 Patients With an Asymmetric Cortical Degenerative Syndrome

Characteristics	Progressive Aphasia Syndrome		Progressive Perceptuomotor Syndromes		Progressive Neuropsychiatric Syndromes		
	Dysfluent	Fluent	R>L*	L>R†	Neuropsychiatric	Spastic	Overall
No. of patients	7	5	5	4	2	3	26
Sex, M:F ratio	2:5	2:3	2:3	0:4	0:2	1:2	7:19
Age at onset of disease, y	66	61	63	57	45	59	60
Time to study, y	4	3.3	4	2.3	2.5	5.7	4
Education, No. of y	12	13	14	15	16	11	13
Handedness, R:L ratio	5:2	5:0	4:1	4:0	2:0	3:0	23:3

*Right lobe more involved than left.
†Left lobe more involved than right.

of the underlying degenerative diseases. Therefore, to facilitate the clinical recognition of ACDS, we summarize our 29-month experience with patients whose clinical condition was dominated by a slowly progressive neurologic syndrome that appeared readily localizable in the cerebrum.

In most instances, the relative focality of the disease was supported by neuroimaging techniques. We also present a clinical classification scheme of ACDS that does not rely on pathologic data.

PATIENTS AND METHODS

All patients who presented with ACDS and who were examined by the behavioral neurology service were selected consecutively between July 1988 and December 1990. *Asymmetric cortical degenerative syndrome* was defined as a slowly progressive (ie, a period of years), localizable neurologic deficit or cortical syndrome that was not caused by a focal structural lesion, such as tumor, vascular impairment or anomaly, demyelination, trauma, or infection. No patient had a history of neurologic disease, except for an unrelated pain syndrome. The demographic data are listed in Table 1.

All patients underwent standard neurologic examination and detailed cognitive and radiologic evaluations. Most patients underwent neuropsychologic examination, and all were examined by a behavioral neurologist (R.J.C. in all but one case). Standardized neuropsychologic tests[27-37] and clinical assessments were performed (Tables 2 and 3); however, not all patients received identical tests. Focal atrophy and hypoperfusion, although often subtle, were demonstrated radiographically with magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) in most patients.

Magnetic resonance imaging was performed at 1.5 T (General Electric, Milwaukee, Wis). To generate surface-rendered images, a three-dimensional volumetric magnetic resonance data set was acquired initially. This was a volumetric gradient echo acquisition measuring 24×24×12 cm in three dimensions, with contiguous cubic 1-mm voxels. This data set was then moved by magnetic tape off line to a stand-alone Sun workstation (Sun Microsystems, Mountain View, Calif). The data were then subjected to a two-dimensional segmentation and edge-extraction operation. Finally, a surface-rendering step was performed. The surface-rendering method has been described previously.[38,39]

Single-photon emission computed tomography was performed with a tomographic scanning camera (General Electric Starcam). Image acquisition was initiated 1 hour after administration of the radiotracer, 20 mC of [technetium-99m] hexamethyl propylene amine oxime (^{99m}Tc-HM-PAO), to an antecubital vein. The patient was placed in the supine position with eyes closed, and 128 frames in a 360° elliptical orbit were obtained with 20 seconds per frame. Tomographic reconstruction was done after prefiltration and attenuation correction. Transaxial sections were generated from the collected data, and coronal and sagittal sections were reconstructed from the transaxial sections. In some patients, the decrease in perfusion apparent on SPECT may reflect loss of tissue volume because of local brain atrophy in addition to a decrease in cerebral blood flow per unit volume of brain tissue.

Neither computed tomography (CT), MRI, nor SPECT was interpreted in a blinded fashion for the purposes of our study. Although focal areas of atrophy may be striking in some cases, they may be subtle and must often be looked for. The diagnosis of ACDS was suspected on a clinical basis, and neuroimaging, obtained in most cases as a clinically necessary part of the diagnostic evaluation, was used to specifically assess the brain areas in question. Nonspecific regions of increased T_2 signal were occasionally encountered in asymptomatic brain regions to the mild degree that is commonly encountered in cognitively normal elderly patients, but in no instance was there evidence of an underlying structural abnormality other than focal atrophy in symptomatic brain regions. No patient with T_1-weighted MRI abnormalities other than cortical atrophy was included in the study.

RESULTS

On the basis of extensive neurologic, linguistic, and cognitive testing, three distinct clinical categories of ACDS were identified: progressive aphasia, progressive perceptuomotor dysfunction, and progressive neuropsychiatric syndromes.

Of the 26 patients studied, 19 were women and seven were men (mean age, 60 years). Three of the patients were left-handed. Six patients had a family history of dementia in a first-, second-, or third-degree relation, and one patient had a son with Tourette's syndrome.

Progressive Aphasia

Twelve patients (eight women and four men) presented with slowly progressive aphasia, which was dysfluent in seven patients and fluent in five. Mean age at onset of disease was 63 years (range, 54 to 73 years). Patients with dysfluent aphasia were slightly older than those with fluent aphasia (Table 1). Ten of the patients were fully right-handed, and two (men with dysfluent aphasia) were fully left-handed. General neurologic examination revealed no evidence of sensorimotor disorders, ideomotor apraxia, pseudobulbar affect, or perseverative tendencies. Cerebrospinal fluid examination was performed in one patient with progressive aphasia (dysfluent), and the results were normal.

Patients with dysfluent aphasia manifested orofacial

Table 2.—Performance of 26 Patients With an Asymmetric Cortical Degenerative Syndrome on the Complex Figure Test, WAIS-R, WMS, WMS-R, and AVLT*

	Scores									
	Complex Figure Test[27]		WAIS-R†[28]			WMS-R[30]		AVLT[31]		
Syndrome/ Patient No. (Date)	Copy	Recall	VIQ‡	PIQ	WMS,[30] MQ	Vel	Vil	Trial 5	Short-term Recall	Delayed Recall
Progressive aphasia										
Dysfluent										
1 (5/89)	35	19	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
1 (2/90)	36	9.5	81	99	101	. . .	. . .	9	8	7
2 (2/89)	34	15.5	86	90	87	. . .	. . .	8	5	5
2 (4/90)	36	13.5	. . .	. . .	. . .	. . .	. . .	9	. . .	5
3	32	17.5	91 (Peabody)	99	. . .	. . .	121	. . .	. . .	. . .
4	35	22.5	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
5 (1/89)	. . .	. . .	70	86	. . .	. . .	. . .	. . .	. . .	. . .
5 (7/90)	32	17.5	65	80	. . .	62	81	4	2	2
6	28	13.5	64	85	. . .	. . .	. . .	6	6	5
7	34	16.5	70	93	. . .	75	119	6	3	4
Fluent										
8	36	16	68	81	68	. . .	. . .	10	6	7
9 (9/87)	. . .	. . .	71	99	79	. . .	. . .	1	1	3
9 (5/89)	34	21.5	54	83	59	. . .	. . .	. . .	. . .	. . .
10	28	7	82	89	72	. . .	. . .	7	5	4
11	35	16	92	108	. . .	86	110	7	7	5
12	34	11	67 (Peabody)	80	. . .	. . .	83	. . .	. . .	. . .
Progressive perceptuomotor syndromes										
R>L										
13 (4/89)	20	6	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
13 (4/90)	5	. . .	92	65	. . .	94	69	6	2	3
14	. . .	. . .	96	80	. . .	. . .	. . .	5	4	2
15	13.5	10.5	97	67	. . .	78	52	7	3	4
16 (2/89)	10.5	. . .	83	71	84	. . .	. . .	8	5	5
16 (5/90)	2.5	1.5	78	59	77	. . .	. . .	5	3	1
17	1	. . .	72	63	. . .	62	. . .	. . .	. . .	. . .
L>R										
18 (7/89)	26.5	5	108	82	. . .	104	. . .	12	10	12
18 (7/90)	22	7	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
19 (12/88)	. . .	. . .	83	68	. . .	64	<50	5	0	2
19 (10/90)	0	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
20	0.5	. . .	84	78	. . .	70	. . .	8	4	5
21 (1/89)	3.5	. . .	88	59	. . .	<50	<50	5	4	2
21 (4/90)	1	. . .	82	61	. . .	65	<50	6	2	4
Progressive neuropsychiatric syndromes										
Neuropsychiatric										
22	32	11.5	80	77	. . .	88	69	9	9	0
23 (10/89)	35	1.5	91	101	. . .	87	77	5	0	0
23 (8/90)	20.5	. . .	82	91	. . .	79	77	0	1	0
Spastic										
24	0	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
25	0	. . .	50 (Peabody)	60	. . .	. . .	. . .	. . .	. . .	. . .
26 (9/89)	12.5	6.5	70	79	. . .	67	72	3	3	2
26 (8/90)	. . .	. . .	75	75	. . .	64	69	4	2	0

*WAIS-R indicates Wechsler Adult Intelligence Scale-Revised; WMS, Wechsler Memory Scale; WMS-R, WMS-Revised; AVLT, Auditory-Verbal Learning Test; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; MQ, memory quotient; Vel, verbal memory index; Vil, visual memory index; and R>L, right hemisphere more involved than left; L>R, left hemisphere more involved than right.

†Age-adjusted standard scores.

‡Three patients received the Peabody Picture Vocabulary Test[29] because aphasia precluded meaningful response on the Wechsler Memory Scale-Revised.

apraxia but not gestural apraxia. There was little evidence of other cognitive deficits in the dysfluent group. Verbal learning was inefficient, but recall of successfully acquired material was relatively preserved. For example, the performance of two patients with dysfluent aphasia was normal on the Craik-Tulving Semantic Encoding Test,[40] which assesses verbal recognition without requiring a spoken response. (Only these two patients were administered the test.) Three of the patients in the dysfluent group also had difficulty with aural comprehension and made semantic errors when tested with a visual naming task. The other patients in the dysfluent group made phonemic and graphemic errors, but they accessed the appropriate lexical tag and did not make semantic substitutions when naming

Table 3.—Performance of 26 Patients With an Asymmetric Cortical Degenerative Syndrome on Several Neuropsychologic Tests*

Syndrome/ Patient No. (Date)	Scores												
	COWA†[32] (Percentiles)	Sentence Repetition[32]	Visual Naming‡	BDAE§[34]	FRT¶[35]	Token Test‖[32]	Short Test of Mental Status		R-L[36]	JLO#[35]	WRAT-R[37]		
							General	Recall			S	A	R
Progressive aphasia													
Dysfluent													
1 (5/89)	17 (1-5)	3/14	Severe	10/10	43	10/22	...	...	17/20	...	...	...	...
1 (2/90)	13 (<1)	0/14	24/60 BNT	10/10	47	...	...	...	...	...	...	...	...
2 (2/89)	25 (6-11)	...	...	10/10	51	...	...	...	...	...	...	...	...
2 (4/90)	25 (6-11)	1/14	50/60 BNT	10/10	48	...	32/38	4/4	20/20	...	...	...	...
3	29 (12-22)	0/14	52/60 BNT	10/10	43	...	...	...	...	...	...	...	...
4		1/14	Normal	10/10	...	Normal	...	...	...	26/30	...	54	66
5 (1/89)	...	...	...	...	...	...	...	...	...	...	...	...	...
5 (7/90)	11 (<1)	Severe	Moderate to mild	1/10	...	28	26/38	4/4	16/20	...	...	...	...
6	...	Severe	37/60 BNT	Normal	...	Mild	26/38	4/4	...	...	68	80	...
7	24 (6-11)	Severe	Severe	6/10	...	...	29/38	3/4	16/20	...	...	...	...
Fluent													
8	23 (1-5)	0/14	Severe	9/10	...	...	...	...	...	...	...	...	63
9 (9/87)	...	...	...	...	...	12/22	27/38	0/4	...	...	...	...	90
9 (5/89)	...	Severe	Severe	...	38	...	26/38	0/4	...	...	...	...	...
10	33 (25-75)	8/14	10/60	Normal	...	37/44	...	...	18/20	...	...	82	87
11	23 (1-5)	3/14	Mild	9/10	48	37/44	36/38	4/4	20/20	...	84	99	...
12	16 (<1)	1/14	16/60 BNT	3/10	...	...	25/38	0/4	...	...	...	...	...
Progressive perceptuomotor syndromes													
R>L													
13 (4/89)	33 (25-75)	...	...	...	Normal	...	25/38	4/4	...	Severe	...	...	...
13 (4/90	...	...	Normal	Normal	...	...	...	...	...	Severe	...	...	104
14	...	...	Normal	Moderate	...	...	20/38	2/4	...	...	...	...	...
15	16 (<1)	8/14	Mild	9/10	...	...	32/38	2/4	...	...	...	76	89
16 (2/89)	Mild	Mild	Normal	Mild	...	Mild	25/38	3/4	...	...	...	...	...
16 (5/90)	17 (<)	...	Normal	...	37	...	19/38	2/4	...	3/30	...	...	...
17	...	...	Mild	9/10	29	Mild	20/38	4/4	...	0/30	...	...	...
L>R													
18 (7/89)	66 (96+)	14/14	Normal	9/10	50	...	37/38	4/4	20/20	19/30	...	...	...
18 (7/90)	64 (96+)	...	...	...	...	Normal	37/38	4/4	...	20/30	...	...	...
19 (12/88)	15 (<1)	10/14	46/60 BNT	Impaired	...	26/44	29/38	4/4	Aphasia	...	...	...	68
19 (10/90)	8 (<1)	5/14	24/60	5/10	Severe	...	21/38	0/4	...	...	...	...	...
20	13 (<1)	6/14	50/60 BNT	9/10	...	...	...	...	20/20	9/30	...	...	85
21 (1/89)	27 (12-22)	8/14	...	8/10	...	...	23/38	2/4	...	...	...	...	...
21 (4/90)	21 (1-5)	5/14	5/9 BNT	...	...	<33	Aphasic	4/4	...	...	...	...	85
Progressive neuropsychiatric syndromes													
Neuropsychiatric													
22	19 (1-5)	Normal	Normal	Normal	Persevere	42	33/38	4/4	...	...	...	70	100
23 (10/89)	28 (12-22)	14/14	Mild	...	36	42	32/38	3/4	...	...	...	...	100
23 (8/90)	27 (12-22)	...	55/60 BNT	...	...	...	28/38	3/4	...	...	...	...	98
Spastic													
24	Severe	0/14	Impaired	Impaired	...	Severe	...	...	...	...	...	...	...
25	Severe	Moderate to severe	Mild	Impaired	Impaired	7/44	...	...	...	...	...	...	...
26 (9/89)	18 (1-5)	...	Mild BNT	Impaired	32	...	21/38	3/4	...	...	...	...	73
26 (8/90)	16 (<1)	...	Mild BNT	Impaired	...	...	21/38	3/4	...	...	...	...	...

*COWA indicates Controlled Oral Word Association Test; BDAE, Boston Diagnostic Aphasia Examination Reading Sentences and Paragraphs; FRT, Facial Recognition Test; R-L, right-left discrimination; JLO, Judgment of Line Orientation; WRAT-R, Wide Range Achievement Test-Revised; S, spelling; A, arithmetic; R, reading; and BNT, Boston Naming Test.

†Corrected scores, given only if test was completed. Patients 1, 3, and 5 gave written responses because of severe dysfluent aphasia. They performed well, indicating that writing per se was not a limiting factor.

‡Stimuli for some patients were from the Boston Naming Test (BNT),[33] as indicated.

§Reading sentences and paragraphs; scored only if test was completed.

¶Age-and education-corrected standard score (54 is highest score), given only if test was completed.

‖No. corrected out of total (44) (total of 22 represents a shorter version of the test), given only if test was completed. Two patients received an abbreviated version.

#Scored only if test was completed.

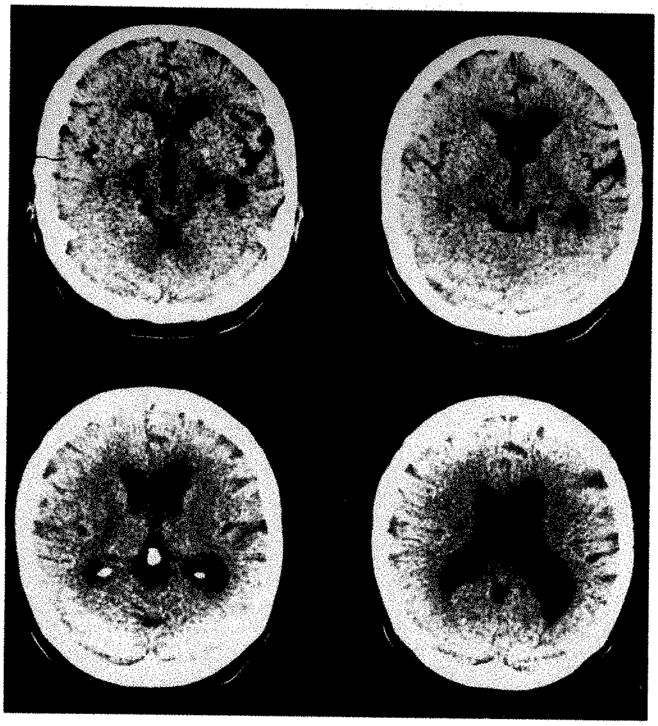

Fig 1.—*Patient 7. Computed tomographic scans of a 66-year-old woman with progressive fluent aphasia of 2 years' duration. Note pronounced atrophy of left temporal lobe and expansion of left lateral ventricle.*

objects, speaking, and writing. The patients were limited only by their difficulty communicating. All of them continued to function relatively normally in their daily routines—maintaining their home, farming, driving, and traveling. At 5 years after the onset of the disease, one patient was still successfully living alone.

The patients with fluent aphasia had much greater difficulty naming objects and made semantic as well as phonemic and graphemic paraphasic errors. One patient stopped working 2 weeks prior to presentation because of difficulty communicating with clients and supervisors but functioned well otherwise. The four other patients continued to work (if employed), drive, and travel and were limited only by their difficulty communicating.

All our patients with ACDS had difficulty writing, but the reason for this was different for each syndrome. Patients with dysfluent aphasia and fluent aphasia made spelling errors, which tended to be more severe in the fluent group. However, writing "praxis" was normal, unlike that of patients with perceptuomotor and neuropsychiatric syndromes who had severe apraxic agraphia.

Two-dimensional MRI and CT showed subtle left perisylvian atrophy in nine patients and moderately severe left hemisphere atrophy with enlargement of the lateral ventricle in one of the patients with fluent aphasia (Fig 1). No asymmetric atrophy was appreciable on MRI in two patients, including one who was left-handed (Table 4). In both patients on whom three-dimensional MRI was performed, focal atrophy was clearly localized to perisylvian language-associated cortices, which was the area suspected clinically to be involved (Fig 2). Single-photon emission computed tomography revealed an asymmetric decrease in cerebral perfusion in left perisylvian cortical and, in some cases, subcortical structures in seven of eight patients (Table 4). Changes were subtle but consistent between cases (Fig 3). No consistent anatomic differences between dysfluent and fluent cases were revealed by SPECT. Anterior and posterior perisylvian regions of hypoperfusion were found in each group.

Seven patients with aphasia underwent electroencephalography (EEG), which showed mild abnormalities in five patients. The abnormality was more severe in the left hemisphere in four patients. Two dysfluent patients underwent electromyography; there was no evidence of motor neuron disease.

Progressive Perceptuomotor Syndromes

Nine patients (seven women and two men) presented with progressive perceptuomotor deficits that indicated dysfunction of either the frontoparietal or the occipitoparietal area. A greater involvement of the right hemisphere was indicated in five patients and of the left hemisphere in four. Patients with mainly right parietal lobe involvement were slightly older (mean age, 63 years) than those with primarily left parietal lobe involvement (mean age, 57 years). Cerebrospinal fluid examination was performed in one patient with a progressive parietal syndrome and showed only a slight increase in total protein value.

Two clinical features were distinctive. First, lateralized somatic deficits were readily detected on physical examination, including hemiparesis or hemispasticity in seven patients, hemisensory deficits in seven, unilateral myoclonic arm jerking in three, and homonymous visual field defects in three patients. None of the patients had cogwheel rigidity or a rest tremor. In six patients, there was an unsteady, narrow-based, and nonshuffling gait; one of these patients was confined to a wheelchair. Second, various forms of apraxia were prominent, ie, constructional apraxia in nine patients, apraxic agraphia in eight, ideational or ideomotor apraxia in eight, and dressing apraxia in seven patients. Language disturbances were present in patients in both the right and the left parietal lobe groups, but they were more severe in the latter group. All patients with progressive parietal lobe syndromes were fluent and, on formal testing (Tables 2 and 3) and in informal conversation, were less impaired than the patients with fluent progressive aphasia. Although learning and memory were impaired, the patients with either progressive parietal lobe or progressive aphasia syndromes were not amnesic.

Spatial perception involving visual and somatesthetic modalities was severely impaired. To assess the visual component of spatial perception, five patients were administered the Facial Recognition Test (FRT) and seven the Judgment of Line Orientation Test (JLO).[35] Performances were generally better on the FRT than on the JLO, supporting the idea that impaired spatial perception is due to parietal lobe dysfunction.[41-43] The somatesthetic aspect of spatial perception was also tested. Tactile object recognition was impaired in four patients (two each in the right and left parietal lobe groups). The impairment was unilateral in three patients and bilateral (worse on the hyperreflexic side) in one patient. Detailed assessment[44] revealed impairment of basic somatesthetic function (two-point discrimination) in one patient and impairment of certain intermediate somatesthetic functions (substance and weight discrimination) with preservation of basic somatesthetic functions in the three other patients. Unilateral median nerve and tibial nerve somatosensory-evoked potential studies were done in three patients (two in the right and one in the left parietal lobe groups) with clinically detectable somatosensory impairment; the results of the

Table 4.—Results of Neuroimaging Studies in 26 Patients With an Asymmetric Cortical Degenerative Syndrome*

Syndrome/Patient No.	Atrophy Seen on CT or MRI	Area of Hypoperfusion Seen on SPECT†
Progressive aphasia		
Dysfluent		
1	L temporal lobe	L frontotemporal area
2	L sylvian fissure widening	L frontotemporal area
3	L frontal operculum	L frontoparietal operculum
4	L frontal operculum, premotor area	L temporal lobe
5	L anterior temporal lobe	L frontotemporal area
6	No focal atrophy	L temporal and L and R frontal lobes
7	L frontotemporoparietal area	NA
Fluent		
8	L>R temporal lobe	NA
9	L temporal lobe	L temporoparietal area
10	L sylvian fissure widening	NA
11	L sylvian fissure widening	Normal
12	No focal atrophy	NA
Progressive perceptuomotor syndromes		
R>L dysfunction		
13	R>L parietal lobe	R>L parieto-occipital area
14	R and L parietal lobes	R>L parieto-occipital area
15	R>L parietal lobe	R>L parieto-occipital area
16	R>L parietal lobe	R>L parieto-occipital area
17	R>L parietal lobe	NA
L>R dysfunction		
18	L parietal lobe	L>R parietal lobe
19	L parietotemporal lobe	L parietotemporal area
20	L inferior parietal lobe	L>R parietal lobe
21	L parietal lobe	NA
Progressive neuropsychiatric syndromes		
Neuropsychiatric syndrome		
22	L and R frontal lobes	L and R frontal and R anterior temporal lobes
23	L and R frontal lobes	NA
Spastic and neuropsychiatric syndrome		
24	L and R frontal lobes	NA
25	L and R frontal lobes	NA
26	L>R frontal lobe	NA

*CT indicates computed tomography; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography; L>R, left side greater than right; R>L, right side greater than left; and NA, not assessed.

†Hypoperfusion of some areas may reflect focal atrophy or reduced cerebral perfusion or both.

studies were normal for all three patients. None of the patients with parietal lobe dysfunction had clinical evidence of hemineglect when tested with panmodality double simultaneous stimulation or with a target cancellation task.[45]

Two-dimensional MRI performed on eight patients revealed asymmetrically severe cortical atrophy that was greater on the clinically suspected side (Table 4). Three-dimensional MRI confirmed the location of the focal atrophic regions in all four patients (one in the right and three in the left parietal lobe subgroups) on whom it was performed (Fig 4). Asymmetric atrophy was indeterminate in a CT study of one patient (patient 14).

Seven patients were studied with SPECT. In each case, there was asymmetric hypoperfusion of the parietal lobes. The hypoperfusion was more severe in the hemisphere associated with the clinically worse symptoms (Table 4). Three patients underwent serial SPECT study each 1 to 2 years apart. These studies showed similar areas of hypoperfusion at 1 to 2 years later, and there was a slight worsening in one case (Fig 5).

In two of five patients, EEG showed mild, asymmetric slowing, which was more severe for the clinically worse hemisphere. In the three other patients, EEG showed mild, bilaterally symmetric dysrhythmic slowing.

Progressive Neuropsychiatric Syndromes

In a series of five patients (four women and one man), two clinical patterns of frontal lobe degeneration were identified. Two patients (mean age, 45 years), evaluated between 2 and 3 years after the onset of disease, presented with a neuropsychiatric syndrome consisting of abulia, perseverative behavior, pseudobulbar affect, and inappropriate dependency on others to care for their daily needs (eg, dressing and washing). Three other patients (mean age, 59 years), examined after a longer duration of disease (mean duration, 5.7 years), presented with prominent, generalized spasticity and similar neuropsychiatric symptoms.

The results of physical examination of the two neuropsychiatric patients were normal, except for the presence of primitive reflexes (snout, palmomental, and glabellar reflexes). At presentation, both patients passed a clinical screening test, including the memory subtest, for dementia[46]; however, detailed neuropsychologic assessment revealed significant memory impairment on more difficult memory tests, disorganized strategy planning, and perseverative tendencies (Tables 2 and 3). One of these patients (patient 22) compulsively went to the bathroom three times during a 1-hour examination and asked to go many more times. The other patient (patient 23) was unable to com-

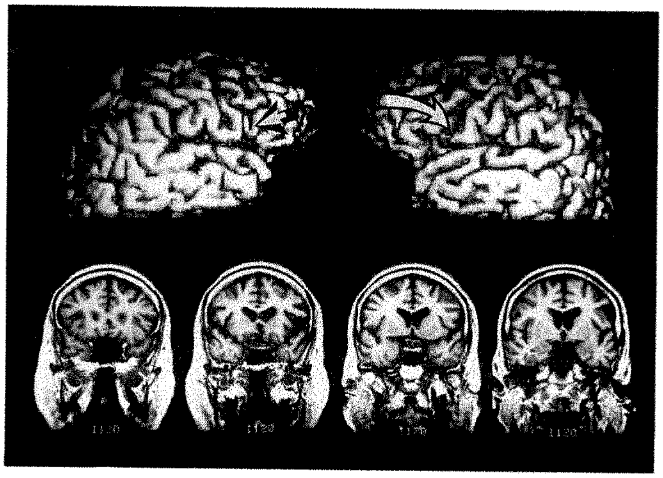

Fig 2.—*Patient 3. Three-dimensional (top) and planar (bottom) magnetic resonance images of focal atrophy of left frontal operculum in case of progressive dysfluent aphasia. Top, Inferior frontal gyrus and pars triangularis appear normal on right (arrow) and atrophic on left (curved arrow). (Used from Caselli et al[63] with permission of Edgell Communications Inc.)*

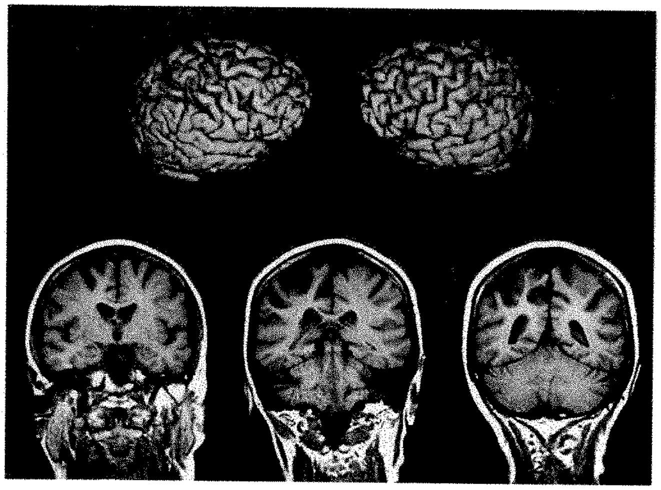

Fig 4.—*Patient 13. Three-dimensional (top) and planar (bottom) magnetic resonance imaging studies of a 64-year-old woman with parietal lobe dysfunction. There is bilateral atrophy of parietal lobes, but atrophy is worse on right and is more pronounced in superior than in inferior parietal lobule. (Used from Caselli et al[63] with permission of Edgell Communications Inc.)*

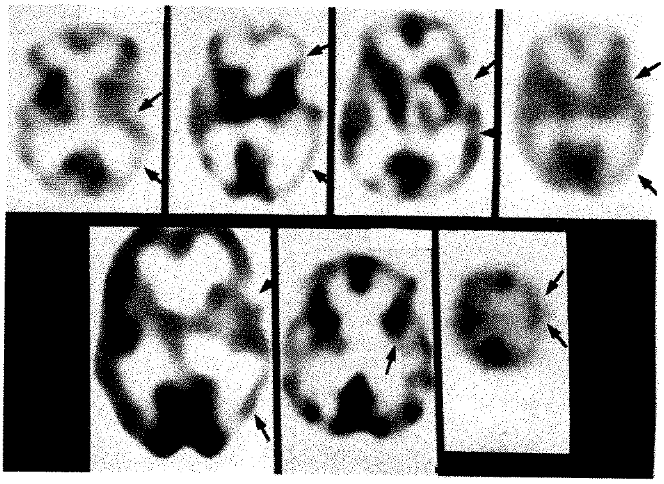

Fig 3.—*Single transverse sections of single-photon emission computed tomography scans of seven patients with progressive aphasia. Top, Scans of patients with dysfluent aphasia. Bottom, Scans of patients with fluent aphasia. Arrows indicate focal areas of relative hypoperfusion in left hemisphere.*

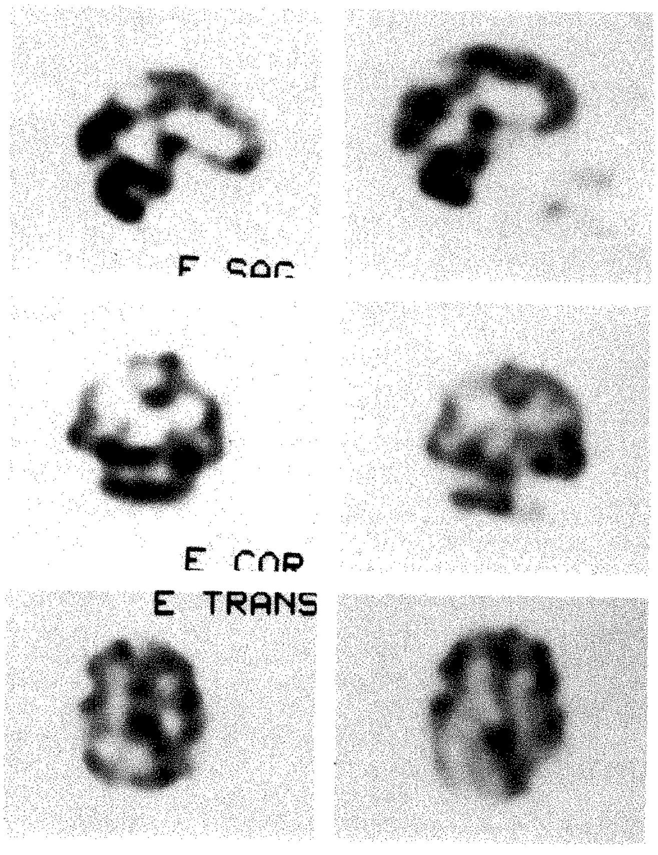

Fig 5.—*Patient 13. Serial single photon emission computed tomographic scans of case in Fig 4. Scans on right were performed 1 year after those on left. Areas of hypoperfusion, pronounced in right superior parietal lobule, correspond to areas of atrophy in Fig 4.*

plete a single category on the Wisconsin Card Sorting Test[47] and made 93 perseverative errors, strongly suggestive of frontal lobe dysfunction. Both patients performed poorly on the Category Test,[48] also consistent with frontal lobe dysfunction.

Changes on CT and MRI were subtle in patient 22 and suggested atrophy of the right frontal and temporal lobes as well as milder atrophy of the left frontal lobe (Fig 6). Clear evidence of hypoperfusion conforming to this distribution of atrophy was found on SPECT (Fig 6). There was a striking pattern of atrophy on MRI in the frontal lobes of the other patient (Fig 7). Findings on EEG were normal in both patients. A biopsy specimen of right prefrontal cortex of a 44-year-old woman (patient 22) revealed mild spongiform atrophy and gliosis of superficial cortical layers (Fig 8). Ultrastructural study of the biopsy specimens suggested slightly increased neuronal lipofuscin. These subtle changes are similar to those described by Mesulam[2] in a patient with progressive aphasia who underwent a left temporal lobe biopsy. The results of a preoperative cerebrospinal fluid examination in this patient were normal, except for a mild increase in total protein value.

The three spastic patients had generalized spasticity, which was slightly worse on one side in two of them, including the presence of a unilateral Babinski sign. One patient, whose condition had progressed for 7 years, could no

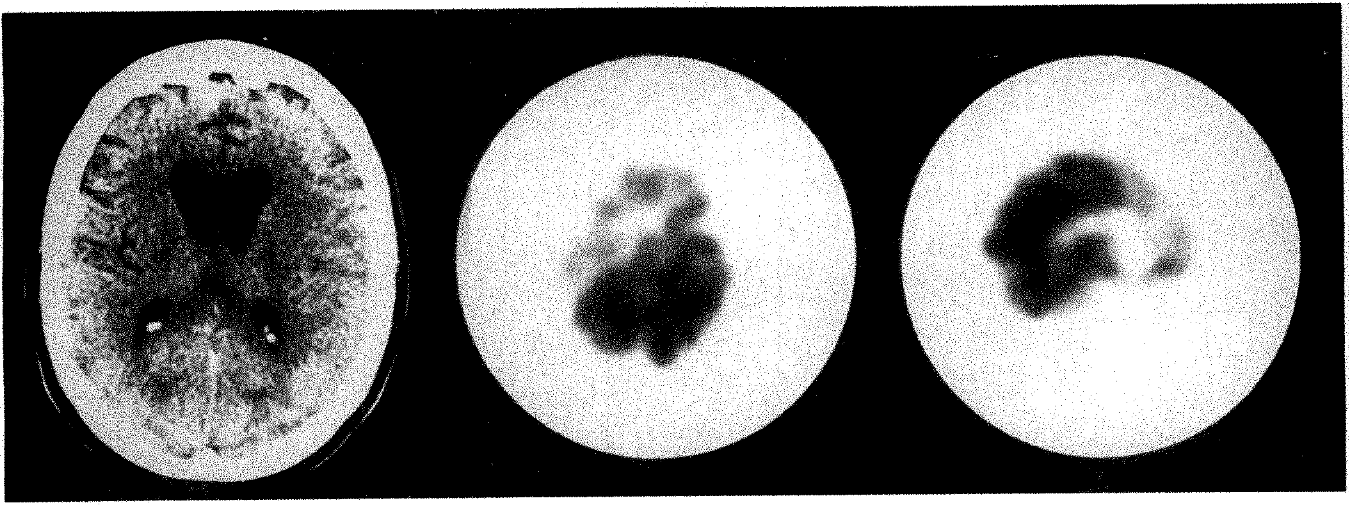

Fig 6.—*Patient 22. Computed tomographic (left) and single photon emission computed tomographic (center and right) scans of 44-year-old woman with progressive neuropsychiatric syndrome. Atrophy of frontal lobes and right temporal lobe is subtle, but center and right scans clearly demonstrate hypoperfusion of these areas.*

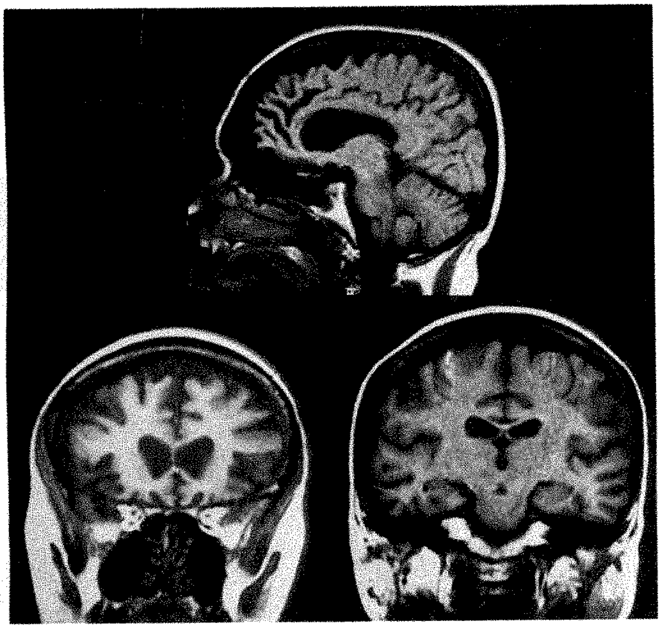

Fig 7.—*Patient 23. Planar magnetic resonance imaging study of 51-year-old woman with 3-year history of neuropsychiatric problems. There is severe atrophy of frontal lobes with widened sulci and dilated frontal horns of lateral ventricles (bottom left). Parietal lobes are relatively spared (bottom right).*

longer walk, but the two other patients could ambulate without assistance. Slightly foreshortened steps suggested a mild gait apraxia in one patient. Pseudobulbar affect, with uncontrollable outbursts of laughing and crying, was prominent in all three patients, as was severe spastic dysarthria (one woman became anarthric 5 years after the onset of the disease). In addition, all three patients had language impairment within the context of general cognitive deterioration (Tables 2 and 3). Verbal associative fluency, aural comprehension, and reading comprehension were severely impaired. Visual naming was impaired only mildly. Writing was both aphasic, with paragraphic and syntactical errors, and apraxic. In addition to apraxic agraphia, patients had severe constructional apraxia and ideomotor apraxia. Despite the unequivocal signs of dementia, the woman who was anarthric was still able to maintain her home effectively and to cook 7 years after the onset of disease. (She died a year later of pneumonia.)

In all three patients with spasticity (Table 4), CT and MRI showed frontal lobe atrophy. None of them were studied with SPECT. Moderate, bitemporal dysrhythmic slowing, worse on the left side, was seen on EEG in one patient. A cerebrospinal fluid examination was performed in one patient, and the results were normal. One spastic patient underwent electromyography; there was no evidence of motor neuron disease.

Longitudinal Neuropsychologic Assessment

Six patients, two in each group, underwent neuropsychologic reassessment, which included the Wechsler Adult Intelligence Scale-Revised,[28] after a mean interval of 14 months (range, 9 to 22 months) (Table 3). Among patients with progressive aphasia, the verbal intelligence quotient (VIQ) decreased from 70.5 to 59.5 and the performance intelligence quotient (PIQ) decreased from 92.5 to 81.5. Among patients with perceptuomotor syndromes, VIQ decreased from 85.5 to 80 and PIQ from 65 to 59.5. Among patients with neuropsychiatric syndromes, VIQ decreased from 80.5 to 78.5 and PIQ from 90 to 83. Similar changes were seen in performance on various other neuropsychologic tests.

Table 5 shows our proposed clinical classification scheme of ACDS based on our observations and on the patient of Tyrrell et al,[19] who had a progressive bitemporal lobe syndrome (greater on right than on left side) characterized predominantly by progressive prosopagnosia. The pathologic correlations listed mainly represent published observations of investigators cited in the introduction.

COMMENT

The slowly progressive cognitive, linguistic, and somatic neurologic deficits of our patients suggested focal pathologic changes that conformed to one of three distinct syndromes: progressive aphasia, progressive perceptuomotor dysfunction, and progressive neuropsychiatric syndrome. Each syndrome could be further divided into two distinct groups: dysfluent and fluent aphasia groups, right and left

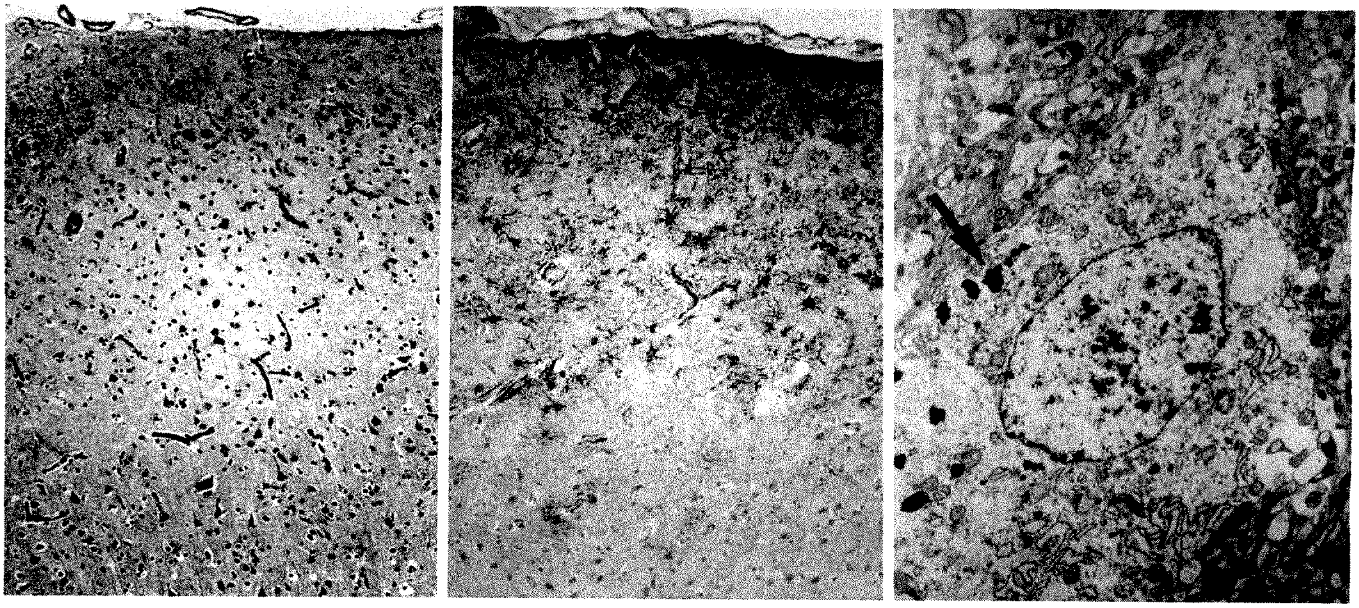

Fig 8.—*Patient 22. Biopsy specimens from right prefrontal area showing mild spongiform degeneration (left) and mild gliosis (center) of superficial cortical layers (hematoxylin-eosin [left]and glial fibrillary acidic protein stain [center]). Electron micrograph (right) of cortical neuron with lipofuscin pigment granules (arrow).*

Table 5.—Clinical Classification of Asymmetric Cortical Degeneration Syndromes*

Syndrome	Brain Topography	Reported Pathology	Other Related Disorders
Progressive aphasia	L perisylvian cortices (L or dominant side)	Nonspecific (mild), nonspecific (spongiform); Alzheimer's, Pick's, neuronal achromasia	MND with aphasic dementia
Dysfluent	L frontal operculum	. . .	. . .
Fluent	L temporal and inferior parietal		
Progressive perceptuomotor	R>L or L>R superior and/or inferior parietal	Nonspecific (spongiform), Alzheimer's	CBD . . .
With hemiparesis	Parietofrontal	. . .	CBD . . .
With hemianopia	Parieto-occipital	. . .	. . .
Progressive neuropsychiatric	R>L, L>R, or L=R frontal	Nonspecific, Pick's	MND with frontal dementia
Neuropsychiatric alone	. . .	. . .	. . .
With spasticity	. . .	. . .	. . .
Prosopagnosia	R>L temporal	Unknown	. . .

*MND indicates motor neuron disease; CBD, corticobasal ganglionic degeneration, R>L, right side greater than left; and L>R, left side greater than right.

parietal lobe groups, and neuropsychiatric and spastic groups. Modern neuroimaging techniques confirmed the clinically suspected location of cortical atrophy and hypoperfusion. Radiographic findings did not specify the cause of the atrophy. However, other contributory factors for cortical degeneration, such as head trauma and encephalitis, were not identified in our patients. Furthermore, the clinical differences between the three syndromes correlated well with the different brain regions that were found to be atrophic and hypoperfused. Patients in whom asymmetric atrophy was discovered serendipitously with neuroimaging studies were not included in our study and without appropriate clinical data cannot be assumed to have ACDS. The diagnosis must be suspected on clinical grounds and neuroimaging results used as supporting evidence.

Superficially, many of the patients in our and other studies of relatively focal cerebral degenerative syndromes meet the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria[49] for a clinical diagnosis of probable Alzheimer's disease. However, closer analysis reveals important qualitative differences between patients with ACDS and those with typical Alzheimer's disease. Although aphasia commonly accompanies Alzheimer's disease, the specific qualities of the aphasia are those of progressively disturbed lexical retrieval with relative preservation of phonetic implementation and syntax, which eventually bears a superficial resemblance to Wernicke's aphasia.[50] Therefore, there is no resemblance between the aphasia of our dysfluent patients and the aphasia of patients with Alzheimer's disease. The fluent aphasia of ACDS more closely resembles the aphasia of advanced Alzheimer's disease. It is the relative severity of the aphasia with little other cognitive disturbance that distinguishes our group of patients from patients with typical Alzheimer's disease. The focal somatic neurologic deficits in the majority of our patients with perceptuomotor syndromes make Alzheimer's disease an unlikely pathologic substrate according to the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related

Disorders Association,[49] despite the exceedingly rare occurrence of Alzheimer's type of pathology in similar previously reported patients.[13,14]

Our patients with frontoparietal dysfunction more closely resembled patients with corticobasal ganglionic degeneration, although they did not have the extrapyramidal signs of rigidity and rest tremor that occur in corticobasal ganglionic degeneration.

The patients with occipitoparietal syndromes bore less resemblance than the patients with frontoparietal syndromes to patients with corticobasal ganglionic degeneration and more closely fit the entity of posterior dementia, which may be associated with nonspecific spongiform atrophy similar to that in patients with progressive aphasia and frontal lobe dementia and Alzheimer's type of pathology.[7,8]

The ACDS patients with perceptuomotor dysfunction had severe apraxic syndromes, with only mild to moderate memory and naming impairments. Although similar types of apraxia occur in patients with Alzheimer's disease, it is generally far less severe than memory and naming impairments,[50] reflecting the earlier and more severe involvement of mesial and temporal structures in Alzheimer's disease.[50-54]

The occurrence of somatic neurologic deficits such as hemiparesis or hemianopia may raise the diagnostic question of cerebrovascular disease simply because of the prevalence of such signs in patients with cerebral infarctions. Although some of our patients, like most elderly patients, had a few areas of abnormal T_2 signal intensity on MRI, these areas were not extensive, were typically periventricular, and were not correlated with the areas of focal cortical atrophy. Although chronic hypoperfusion may occasionally cause a focal deficit with stuttering progression, it has not been demonstrated to result in the steady and inexorable progressive deterioration that our patients experienced. Further, none of our patients had any clinical symptoms suggestive of "hemodynamic" transient cerebral ischemia. The areas of atrophy in some of the patients with perceptuomotor syndromes were in cerebrovascular watershed territories, but this was not true for any of the patients with progressive aphasia or neuropsychiatric syndromes. Because the time course of disease progression, the radiologic findings, and, in many cases, the neuropathologic features of the different patient groups were similar, there is currently no reason to believe that the perceptuomotor patients have different pathophysiologic features than do the other groups.

In the ACDS patients with neuropsychiatric syndromes, the relative degrees of differential impairment are most notable. On simple memory tests (short test of mental status),[46] no impairment was evident despite pronounced frontal lobe features that included affective outbursts, abulia, spasticity, and impaired verbal associative fluency. Radiologic and histopathologic features further support considering these patients distinct from patients with Alzheimer's disease. Our patients more closely resembled patients with Pick's disease and frontal lobe dementia. No lower motor neuron signs were detectable clinically or electrophysiologically; thus, these patients did not have frontal lobe dementia associated with motor neuron disease. The pathologic features were not distinctive in our patient and resembled findings in patients with frontal lobe dementia,[3,5] motor neuron disease with dementia,[19,55,56] and progressive aphasia.[2] Last, certain common features of Alzheimer's disease were absent in all our patients, including anosognosia and paranoid delusional behavior.

The above clinical features justify treating these patients as clinically distinctive. They do not resemble patients with Alzheimer's disease and are not the commonly seen variants that occur in the context of typical Alzheimer's disease. Nonetheless, previous studies showed that some such patients ultimately meet the pathologic criteria for Alzheimer's disease. Neuropathologic hallmarks of Alzheimer's disease are nonspecific, and there are many causes of neurofibrillary tangles.[57-62] Because of the variety and nonspecificity of pathologic substrates involved and because of the range of clinical manifestations of a single histopathologic pattern, nosologic relationships between all of the underlying pathologic entities are presently unclear. Nonetheless, a rational clinical approach is needed to aid in diagnosis, to aid in understanding the clinical course of these conditions over time, and to add greater relevance to clinicopathologic correlations, which are vital to further understanding of these conditions and why they differ from more common patterns of dementia.

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Re-introduce the oldest advance in medicines. Make talking a crucial part of your practice. Because good, clear communication about medicines isn't a thing of the past. It's the way to a healthier future.

Before they take it, talk about it.

National Council on
Patient Information and Education.
666 Eleventh St. N.W. Suite 810
Washington, D.C. 20001

Dilantin® Kapseals®

(extended phenytoin sodium capsules, USP) 100 mg

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See "Warnings" section for information on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, and immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Caution – Federal law prohibits dispensing without prescription. 0362G280

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References **1.** Data on file, Market Research Dept, Parke-Davis. **2.** Ramsay RE, Wilder BJ, Berger JR, Bruni J. A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology*. 1983;33:904-910. **3.** Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin T. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *J Neurol Neurosurg Psychiatry*. 1985;48:639-644. **4.** Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med*. 1985;313:145-151.

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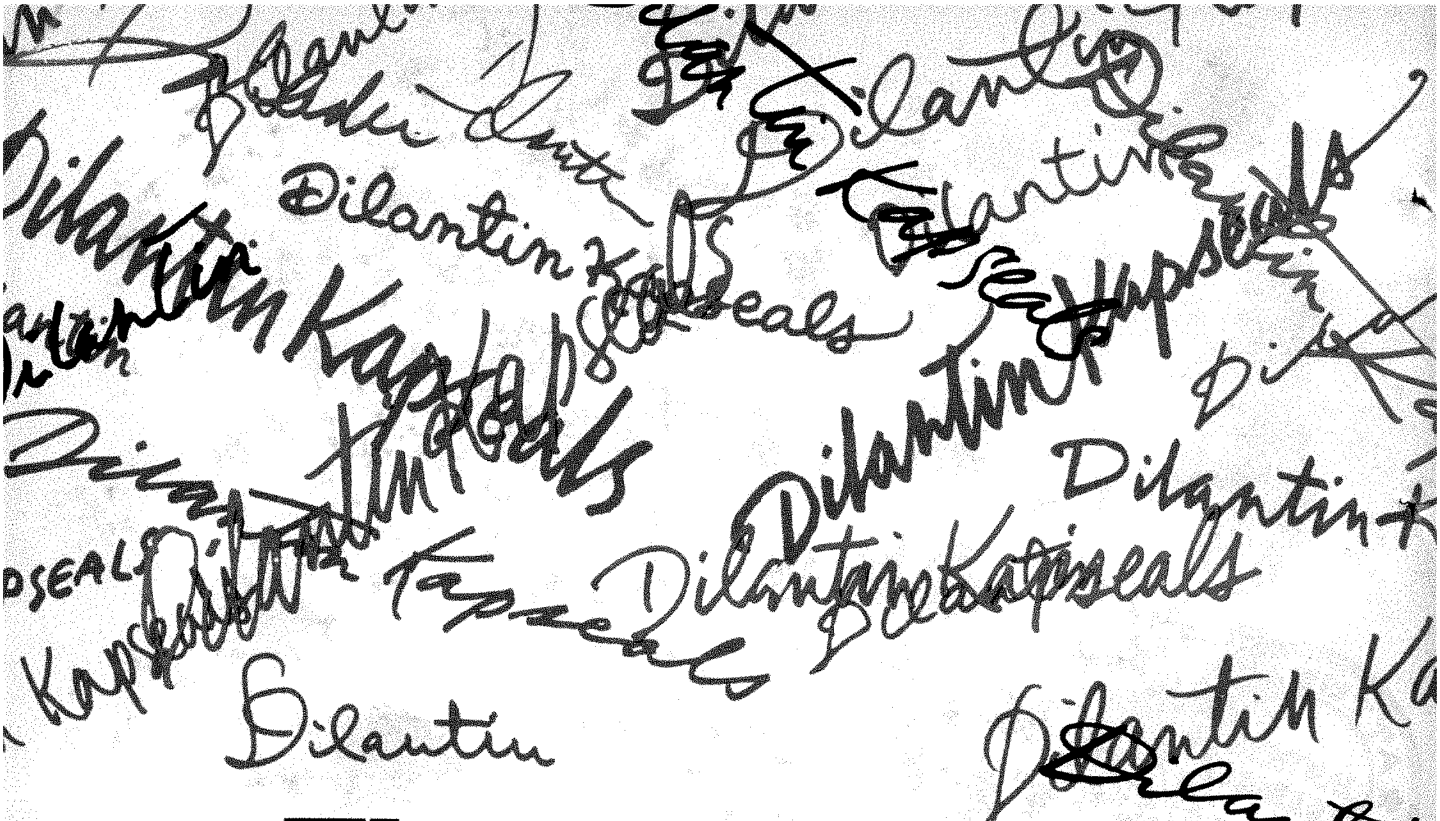

Thousands of neurologists go by the same name.

Neurologists write "Dilantin" more often than any other name in anticonvulsant therapy[1]—and for good reasons:

- **Unsurpassed control of generalized and partial seizures[2-4]**
- **Convenient once-daily dosing for many patients***
- **Significantly lower cost than carbamazepine or valproic acid[†]**

When you add billions of successful patient therapy days, it's clear why so many neurologists independently write the same prescription: Dilantin Kapseals for effective seizure control.

*For adult patients already controlled on 100 mg tid of Dilantin Kapseals.
[†] Adapted from *IMS National Pharmacy Audit Basic Data Book*, 4/91-6/91.[1]
Please see next page for a brief summary of full prescribing information.

Dilantin® Kapseals®

(extended phenytoin sodium capsules, USP) 100 mg

For control, compliance, and cost

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B. D. Moore III, D. R. Copeland, H. Ried, B. Levy

Cerebral White Matter and Cognition in Hydrocephalic Children

J. M. Fletcher, T. P. Bohan, M. E. Brandt, B. L. Brookshire, S. R. Beaver, D. J. Francis, K. C. Davidson, N. M. Thompson, M. E. Miner

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Magnetic Resonance Imaging Signal Hyperintensities in the Deep and Subcortical White Matter: A Comparative Study Between Stroke Patients and Normal Volunteers

R. Schmidt, F. Fazekas, G. Kleinert, H. Offenbacher, K. Gindl, F. Payer, W. Freidl, K. Niederkorn, H. Lechner

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Neuropsychiatric Correlates of Cerebral White-Matter Radiolucencies in Probable Alzheimer's Disease

O. L. Lopez, J. T. Becker, D. Rezek, J. Wess, F. Boller, C. F. Reynolds III, M. Panisset

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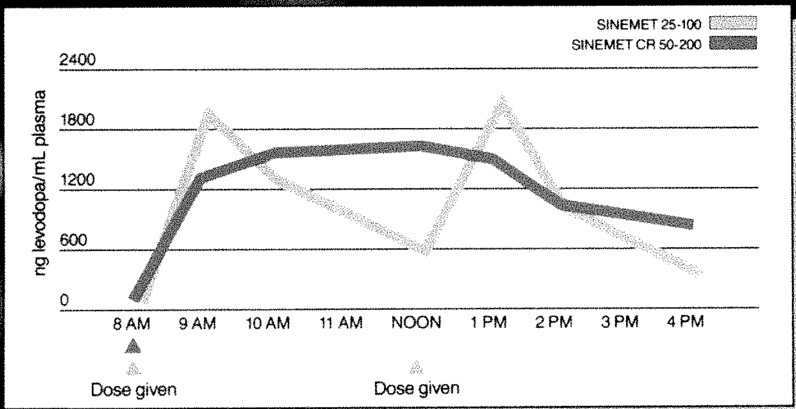
Volume 49, Number 8

American Medical Association
Physicians dedicated to the health of America

For many patients with
Parkinson's disease

More Quality Time*

The causes of motor fluctuations are not completely understood; *in some patients* they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.



Smoother plasma levodopa levels[†1]

Less fluctuation of plasma levodopa levels with SINEMET CR vs SINEMET® (Carbidopa-Levodopa)

In a clinical trial, 14 patients with mild to moderate Parkinson's disease had plasma levodopa levels measured over 8 hours after one dose of SINEMET CR, and were compared with levels over the same period after two doses of SINEMET 25-100.

SINEMET® CR
(CARBIDOPA-LEVODOPA)
SUSTAINED-RELEASE

Before prescribing SINEMET CR, please see a Brief Summary of Full Prescribing Information on the third page of this advertisement.

®SINEMET is a registered trademark of Merck & Co., Inc., Rahway, NJ, USA
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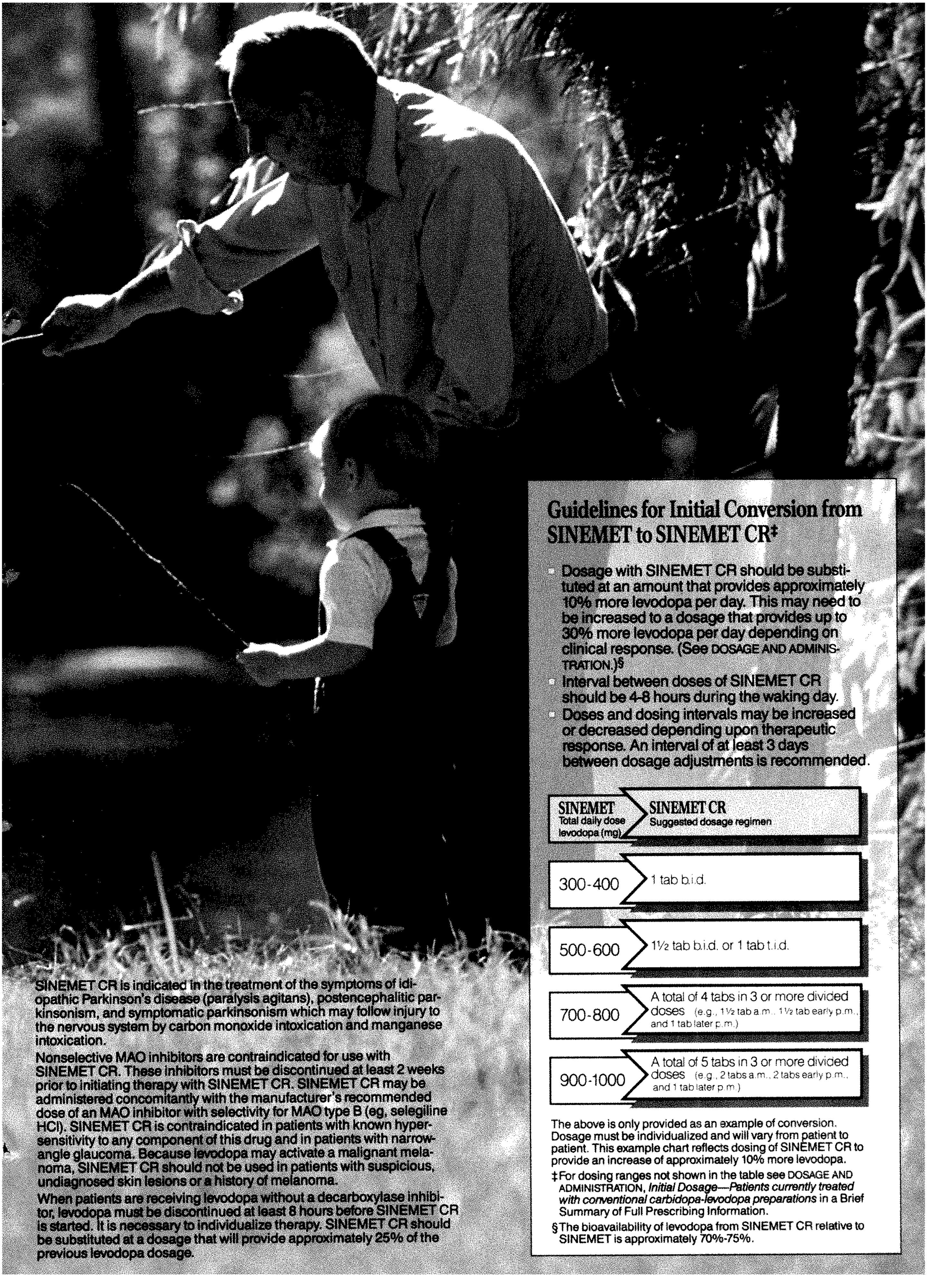
* Although in clinical trials, patients with moderate to severe motor fluctuations who received SINEMET® CR (Carbidopa-Levodopa) Sustained-Release *did not experience quantitatively significant reductions* in "off" time when compared to SINEMET, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET.

† Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET. The physician should be notified if such delayed responses pose a problem in treatment.

1. Goetz CG, Tanner CM, Shannon KM, et al. Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuations. *Neurology.* 1988;38:1143-1146.



SINEMET CR is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication.

Nonselective MAO inhibitors are contraindicated for use with SINEMET CR. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (eg, selegiline HCl). SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma. Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least 8 hours before SINEMET CR is started. It is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage.

Guidelines for Initial Conversion from SINEMET to SINEMET CR‡

- Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day. This may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response. (See DOSAGE AND ADMINISTRATION.)§
- Interval between doses of SINEMET CR should be 4-8 hours during the waking day.
- Doses and dosing intervals may be increased or decreased depending upon therapeutic response. An interval of at least 3 days between dosage adjustments is recommended.

SINEMET Total daily dose levodopa (mg)	**SINEMET CR** Suggested dosage regimen
300-400	1 tab b.i.d.
500-600	1½ tab b.i.d. or 1 tab t.i.d.
700-800	A total of 4 tabs in 3 or more divided doses (e.g., 1½ tab a.m., 1½ tab early p.m., and 1 tab later p.m.)
900-1000	A total of 5 tabs in 3 or more divided doses (e.g., 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

The above is only provided as an example of conversion. Dosage must be individualized and will vary from patient to patient. This example chart reflects dosing of SINEMET CR to provide an increase of approximately 10% more levodopa.

‡ For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage—Patients currently treated with conventional carbidopa-levodopa preparations* in a Brief Summary of Full Prescribing Information.

§ The bioavailability of levodopa from SINEMET CR relative to SINEMET is approximately 70%-75%.

SINEMET® CR (CARBIDOPA-LEVODOPA)
SUSTAINED-RELEASE TABLETS

CONTRAINDICATIONS Nonselective MAO inhibitors are contraindicated for use with SINEMET* CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl).

SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least eight hours before SINEMET CR is started. In order to reduce adverse reactions, it is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION).

Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, will occur at lower dosages and sooner during therapy with SINEMET CR (Carbidopa-Levodopa, Sustained-Release) than with levodopa alone.

As with levodopa, SINEMET CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution. The occurrence of dyskinesias may require dosage reduction.

Patients receiving SINEMET CR may develop increased dyskinesia compared to SINEMET (Carbidopa-Levodopa).

SINEMET CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET CR to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET CR may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

PRECAUTIONS General As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET CR provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Information for Patients The patient should be informed that SINEMET CR is a sustained-release formulation of carbidopa-levodopa which releases these ingredients over a 4 to 6 hour period. It is important that SINEMET CR be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

If abnormal involuntary movements appear or get worse during treatment with SINEMET CR, the physician should be notified, as dosage adjustment may be necessary.

Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET (Carbidopa-Levodopa). The physician should be notified if such delayed responses pose a problem in treatment.

Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.

NOTE: The suggested advice to patients being treated with SINEMET CR is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Laboratory Tests Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa-levodopa preparations than with levodopa.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions *Caution should be exercised when the following drugs are administered concomitantly with SINEMET CR (Carbidopa-Levodopa, Sustained-Release).*

Symptomatic postural hypotension has occurred when carbidopa-levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with SINEMET CR is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET CR should be carefully observed for loss of therapeutic response.

Carcinogenesis, Mutagenesis, Impairment of Fertility In a two-year bioassay of SINEMET (Carbidopa-Levodopa), no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

In reproduction studies with SINEMET (Carbidopa-Levodopa), no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

Pregnancy Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET (Carbidopa-Levodopa). There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. SINEMET (Carbidopa-Levodopa) caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. Use of SINEMET CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINEMET CR is administered to a nursing mother.

Pediatric Use Safety and effectiveness in infants and children have not been established, and use of the drug in patients below the age of 18 is not recommended.

ADVERSE REACTIONS In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations while on SINEMET (Carbidopa-Levodopa) were randomized to therapy with either SINEMET (Carbidopa-Levodopa) or SINEMET CR. The adverse experience frequency profile of SINEMET CR did not differ substantially from that of SINEMET (Carbidopa-Levodopa), as shown in Table 1.

Table 1 Clinical Adverse Experiences Occurring in 1% or Greater of Patients

Adverse Experience	**SINEMET CR** n=491 %	**SINEMET** (Carbidopa-Levodopa) n=524 %
Dyskinesia	16.5	12.2
Nausea	5.5	5.7
Hallucinations	3.9	3.2
Confusion	3.7	2.3
Dizziness	2.9	2.3
Depression	2.2	1.3
Urinary Tract Infection	2.2	2.3
Headache	2.0	1.9
Dream Abnormalities	1.8	0.8
Dystonia	1.8	0.8
Vomiting	1.8	1.9
Upper Respiratory Infection	1.8	1.0
Dyspnea	1.6	0.4
'On-Off' Phenomena	1.6	1.1
Back Pain	1.6	0.6
Dry Mouth	1.4	1.1
Anorexia	1.2	1.1
Diarrhea	1.2	0.6
Insomnia	1.2	1.0
Orthostatic Hypotension	1.0	1.1
Shoulder Pain	1.0	0.6
Chest Pain	1.0	0.8
Muscle Cramps	0.8	1.0
Paresthesia	0.8	1.1
Urinary Frequency	0.8	1.1
Dyspepsia	0.6	1.1
Constipation	0.2	1.5

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received SINEMET CR and 475 who received SINEMET (Carbidopa-Levodopa) during controlled clinical trials included: decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.

The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with SINEMET CR, listed by body system in order of decreasing frequency, include:

Nervous System/Psychiatric: Chorea, somnolence, falling, anxiety disorder, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.

Body as a Whole: Asthenia, fatigue, abdominal pain, orthostatic effects.

Digestive: Gastrointestinal pain, dysphagia, heartburn.

Cardiovascular: Palpitation, essential hypertension, hypotension, myocardial infarction.

Special Senses: Blurred vision.

Metabolic: Weight loss.

Skin: Rash.

Respiratory: Cough, pharyngeal pain, common cold.

Urogenital: Urinary incontinence.

Musculoskeletal: Leg pain.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

Other adverse experiences have been reported with various carbidopa-levodopa formulations and may occur with SINEMET CR:

Nervous System/Psychiatric: Mental changes including paranoid ideation, psychotic episodes, depression with suicidal tendencies and dementia; convulsions (however, a causal relationship has not been established); bradykinetic episodes.

Gastrointestinal: Gastrointestinal bleeding, development of duodenal ulcer.

Cardiovascular: Cardiac irregularities, phlebitis.

Hematologic: Hemolytic and nonhemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.

Laboratory Tests: Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, protein-bound iodine, Coombs test.

Other adverse reactions that have been reported with levodopa are:

Nervous System: Numbness, increased hand tremor, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome.

Psychiatric: Delusions, euphoria.

Gastrointestinal: Bitter taste, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.

Metabolic: Weight gain, edema.

Integumentary: Malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, loss of hair.

Genitourinary: Urinary retention, urinary incontinence, dark urine, priapism.

Miscellaneous: Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE Management of acute overdosage with SINEMET CR is the same as with levodopa. Pyridoxine is not effective in reversing the actions of SINEMET CR.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET CR should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION SINEMET CR tablets contain carbidopa (50 mg) and levodopa (200 mg) in a 1:4 ratio. The daily dosage of SINEMET CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of involuntary movements, dyskinesias or nausea. SINEMET CR may be administered as whole or as half-tablets which should not be chewed or crushed.

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while SINEMET CR is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Initial Dosage *Patients currently treated with conventional carbidopa-levodopa preparations:* Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see DOSAGE AND ADMINISTRATION, TITRATION). The interval between doses of SINEMET CR should be 4-8 hours during the waking day. *Patients currently treated with levodopa without a decarboxylase inhibitor:* Levodopa must be discontinued at least eight hours before therapy with SINEMET CR is started. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET CR b.i.d. *Patients not receiving levodopa:* In patients with mild to moderate disease, the initial recommended dose is 1 tablet of SINEMET CR b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with 2 to 8 tablets per day, administered as divided doses at intervals ranging from 4 to 8 hours during the waking day. Higher doses (12 or more tablets per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day.

An interval of at least 3 days between dosage adjustments is recommended.

Maintenance Because Parkinson's disease is progressive, periodic clinical evaluations are recommended; adjustment of the dosage regimen of SINEMET CR may be required.

Addition of Other Antiparkinson Medications Anticholinergic agents, dopamine agonists, and amantadine can be given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added.

A dose of SINEMET (Carbidopa-Levodopa) 25-100 or 10-100 (one half or a whole tablet) can be added to the dosage regimen of SINEMET CR in selected patients with advanced disease who need additional levodopa for a brief time during daytime hours.

Interruption of Therapy Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET CR is required, especially if the patient is receiving neuroleptics. (See WARNINGS).

If general anesthesia is required, SINEMET CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED SINEMET CR 50-200 (Carbidopa-Levodopa) SUSTAINED-RELEASE TABLETS containing 50 mg of carbidopa and 200 mg of levodopa, are peach-colored, oval, scored, biconvex, compressed tablets, coded 521. They are supplied as follows:

NDC 0056-0521-68 bottles of 100
NDC 0056-0521-28 unit dose packages of 100.

Storage Avoid temperatures above 30°C (86°F). Store in a tightly closed container.

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Brief Summary of 6251-3/7619403 CR-31238

TABLETS

SINEMET® (CARBIDOPA-LEVODOPA)

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS (below) and DOSAGE AND ADMINISTRATION sections in the Prescribing Information before initiating therapy.

INDICATIONS: SINEMET is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication. SINEMET is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B_6).

The incidence of levodopa-induced nausea and vomiting is less with SINEMET than with levodopa. In many patients this reduction in nausea and vomiting will permit more rapid dosage titration.

In some patients a somewhat smoother antiparkinsonian effect results from therapy with SINEMET than with levodopa. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from SINEMET.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Although the administration of carbidopa permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa. *Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, may occur at low dosages and sooner during therapy with SINEMET than with levodopa.*

Certain patients who responded poorly to levodopa have improved when SINEMET was substituted. This is most likely due to decreased peripheral decarboxylation of levodopa which results from administration of carbidopa rather than to a primary effect of carbidopa on the nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa in parkinsonian syndromes.

In considering whether to give SINEMET to patients already on levodopa who have nausea and/or vomiting, the practitioner should be aware that, while many patients may be expected to improve, some do not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing SINEMET with levodopa, about half of the patients with nausea and/or vomiting on levodopa improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

CONTRAINDICATIONS: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See DOSAGE AND ADMINISTRATION section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

PRECAUTIONS: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS (above).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

ADVERSE REACTIONS: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitation, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred.

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, protein-bound iodine, and Coombs test.

Other adverse reactions that have been reported with levodopa are: *Nervous System:* ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome. *Psychiatric:* confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria. *Gastrointestinal:* dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue. *Metabolic:* weight gain or loss, edema. *Integumentary:* malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, skin rash, loss of hair. *Genitourinary:* urinary retention, urinary incontinence, dark urine, priapism. *Special Senses:* diplopia, blurred vision, dilated pupils, oculogyric crises. *Miscellaneous:* weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

HOW SUPPLIED: Tablets SINEMET 10-100, SINEMET 25-100, and SINEMET 25-250 are supplied in bottles of 100 and unit dose packages of 100.

Storage: Tablets SINEMET 10-100 and Tablets SINEMET 25-250 must be protected from light.

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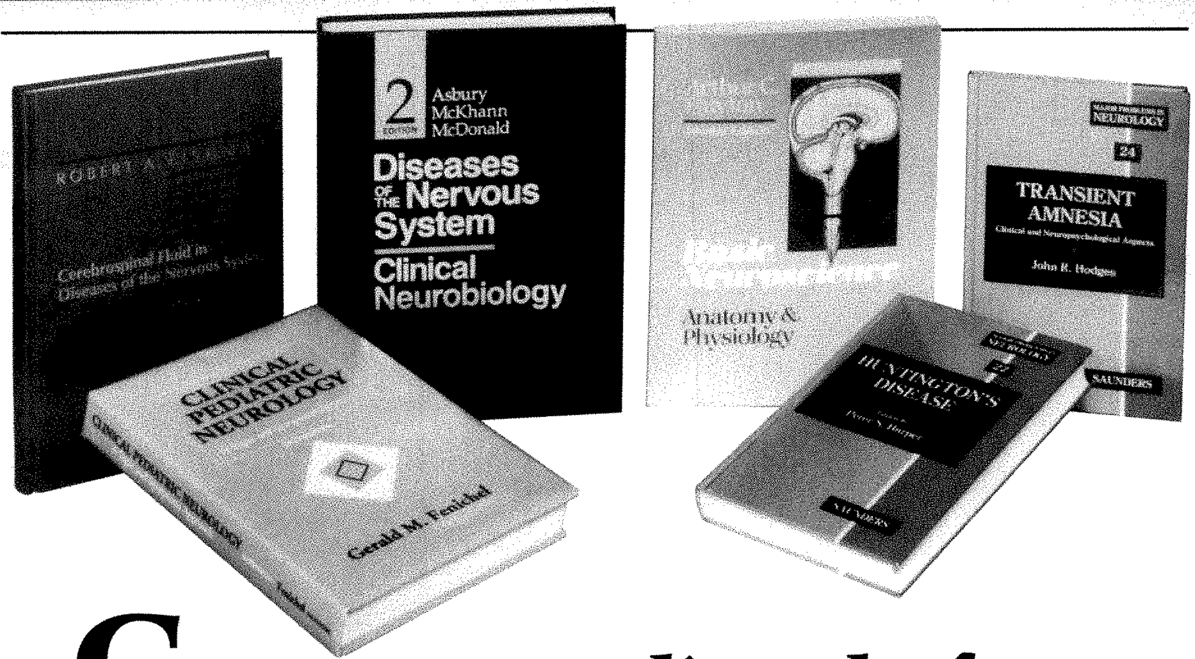

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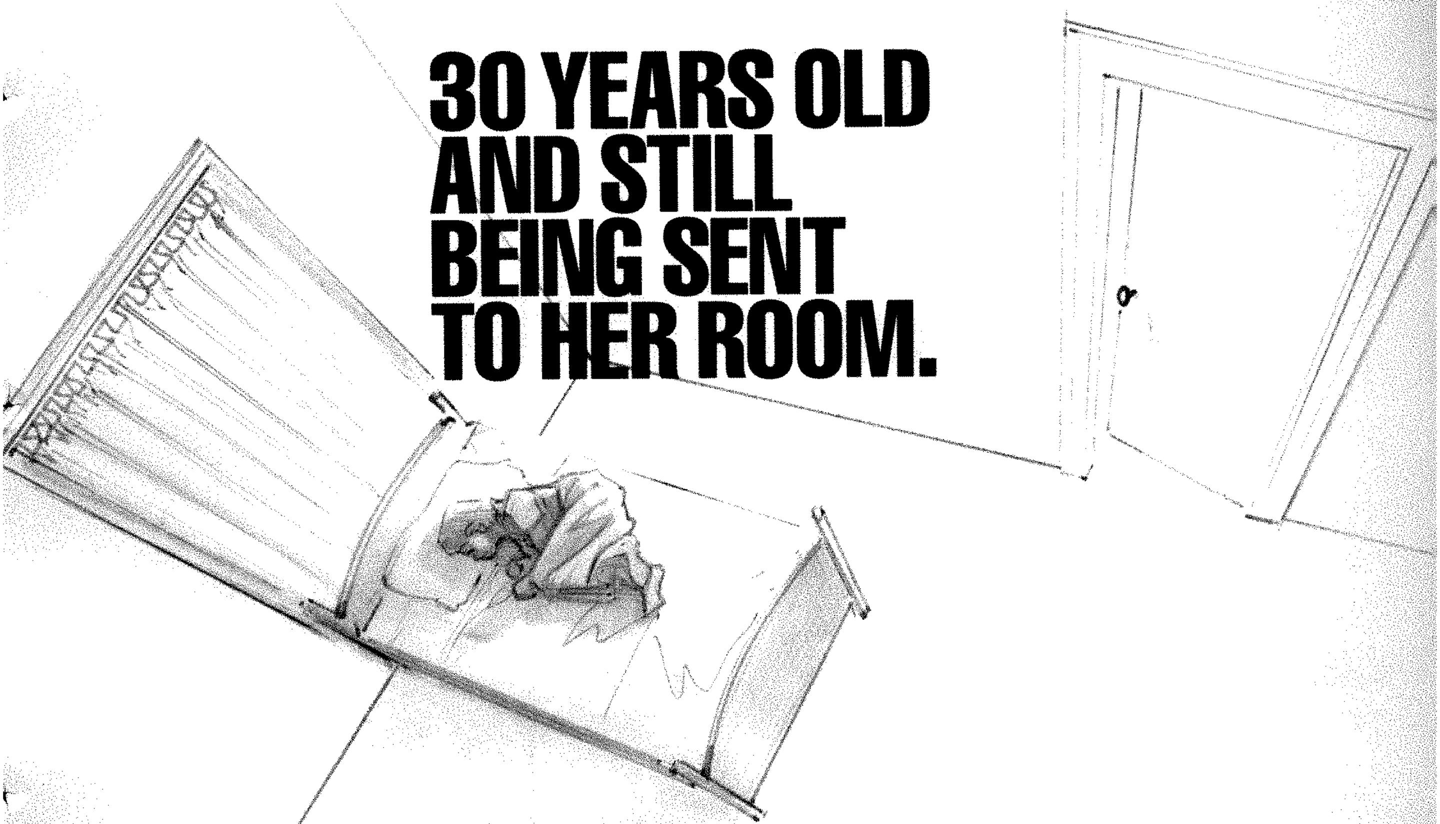

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INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma.

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Please see brief summary on next page.
63284

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anagement of **Hypertrophic Subaortic Stenosis** — especially for treatment of exertional or other stress-induced igina, palpitations, and syncope. INDERAL LA also improves exercise performance. Clinical improvement may be mporary.

)NTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than st-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS), unless the failure is secondary a tachyarrhythmia treatable with INDERAL.

ARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory funcon in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. though beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close llow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. ta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to rdiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated th diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

N PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, nyocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of NDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be autioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other neasures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be inrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult therosclerotic heart disease who are given propranolol for other indications.

)nallergic Bronchospasm (eg, chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISSES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it ay block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

AJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controrsial. It should be noted that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the ks of general anesthesia and surgical procedures.

DERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by ministration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted vere hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

ABETES AND HYPOGLYCEMIA: Use beta blockers with caution in diabetic patients if a beta-blocking agent is required. ta blockers may mask tachycardia occurring with hypoglycemia; other manifestations such as dizziness and sweating ay not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery blood glucose to normal levels.

IYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism, thus abrupt withdrawal of proanolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may ange thyroid-function tests, increasing T_4 and reverse T_3, and decreasing T_3.

PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after proanolol, tachycardia was replaced by severe bradycardia requiring a demand pacemaker. In one case this resulted after initial dose of 5 mg propranolol.

IECAUTIONS. GENERAL: Use with caution in patients with impaired hepatic or renal function. INDERAL is not indicated the treatment of hypertensive emergencies.

ta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may erfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

INICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum insaminase, alkaline phosphatase, lactate dehydrogenase.

IUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting mpathetic nervous activity resulting in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic potension.

ution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, pecially intravenous verapamil, as both agents may depress myocardial contractility or atrioventricular conduction. On e occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reacns, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

uminum hydroxide gel greatly reduces intestinal absorption of propranolol.

hanol slows the rate of absorption of propranolol.

ienytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

ilorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

itipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

iyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

metidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

ieophylline clearance is reduced when used concomitantly with propranolol.

IRCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: There was no evidence of significant drug-induced icity in rats or mice, employing doses up to 150 mg/kg/day over an 18-month period. There were no drug-related norigenic effects at any dosage levels. No impairment of fertility attributable to the drug was seen in animal reproduce studies.

IEGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 ies greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnt women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

IRSING MOTHERS: INDERAL is excreted in human milk. Exercise caution when INDERAL (propranolol HCl) is adminered to a nursing woman.

DIATRIC USE: Safety and effectiveness in children have not been established.

IVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of erapy.

rdiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; rombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

intral Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; versible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute versible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, ghtly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, hargy, and vivid dreams appear dose related.

istrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial rombosis, ischemic colitis.

lergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, larynspasm, and respiratory distress.

spiratory: Bronchospasm.

imatologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

ito-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

iscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have en reported rarely. The oculomucocutaneous reactions associated with practolol have not been reported with opranolol.

ISAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for ministration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg bstitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necesry, especially to maintain effectiveness at the end of the 24-hour dosing interval.

r management of hypertension, angina pectoris, migraine, and hypertrophic subaortic stenosis the dosage must be lividualized. Usual initial dose is 80 mg once daily. **For complete dosage information see package literature.**

reatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

DIATRIC DOSAGE – At this time the data on the use of the drug in this age group are too limited to permit adequate ections for use.

IERDOSAGE. INDERAL is not significantly dialyzable. If ingestion is, or may have been, recent, evacuate gastric conits, taking care to prevent pulmonary aspiration.

IADYCARDIA: Administer atropine (0.25 to 1.0 mg); if no response to vagal blockade, administer isoproterenol utiously. CARDIAC FAILURE: digitalization and diuretics. HYPOTENSION: vasopressors, eg, levarterenol or inephrine (there is evidence that epinephrine is the drug of choice). BRONCHOSPASM: administer isoproterenol and iinophylline.

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such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: Either 200 mg b.i.d. for tablets or 1 teaspoon q.i.d. for suspension (400 mg per day). Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: Either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension (200 mg per day). Increase at weekly intervals by adding up to 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg/daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100 .... NDC 58887-052-30
Unit Dose (blister pack)
  Box of 100
  (strips of 10) .... NDC 58887-052-32

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

  Bottles of 100 .... NDC 58887-027-30
  Bottles of 1000 .... NDC 58887-027-40
Unit Dose (blister pack)
  Box of 100
  (strips of 10) .... NDC 58887-027-32

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture. Dispense in tight container (USP).

Suspension 100 mg/5 ml (teaspoon)—yellow-orange, citrus-vanilla flavored

  Bottles of 450 ml .... NDC 58887-019-76

Shake well before using.
Do not store above 86°F.
Dispense in tight, light-resistant container (USP).

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BASEL Pharmaceuticals

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Division of
CIBA-GEIGY Corporation
Summit, New Jersey 07901

Dosage Information: Tablets and Suspension

Indication	Initial Dose		Subsequent Dose		Maximum Dose
	Tablet	Suspension	Tablet	Suspension	Tablet or Suspension
Epilepsy					
6-12 years of age	100 mg b.i.d. (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 100 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 1 teaspoon (100 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours
Over 12 years of age	200 mg b.i.d. (400 mg/day)	1 teaspoon q.i.d. (400 mg/day)	Add up to 200 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 2 teaspoons (200 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours: 12-15 years 1200 mg/24 hours: over 15 years 1600 mg/24 hours: adults, in rare instances
Trigeminal Neuralgia	100 mg b.i.d. on the first day (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 200 mg per day in increments of 100 mg every 12 hours	Add up to 2 teaspoons (200 mg) per day q.i.d.	1200 mg/24 hours

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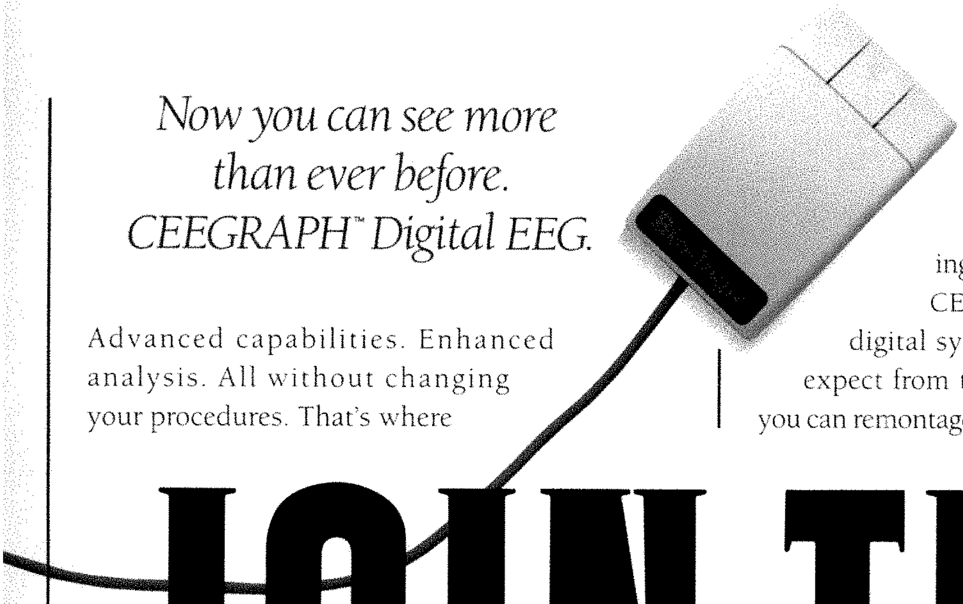

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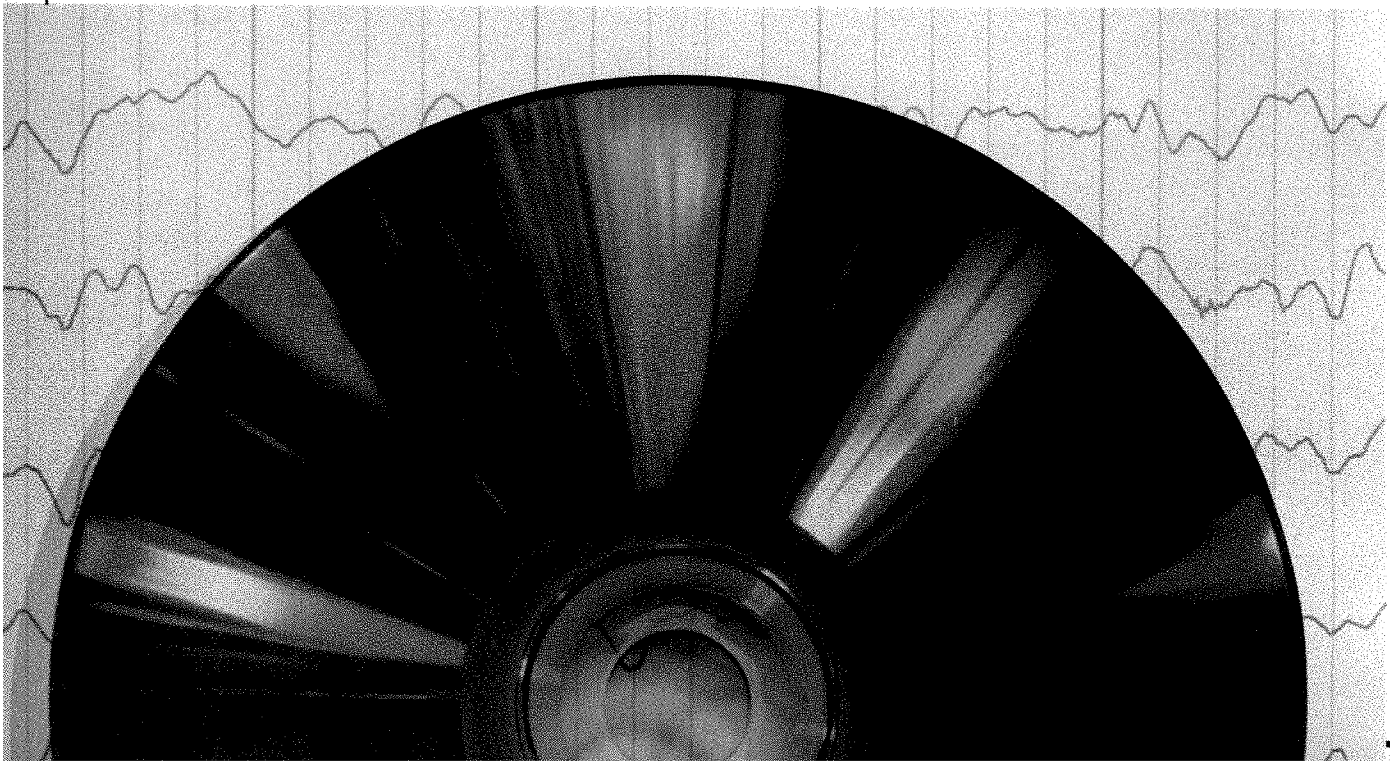

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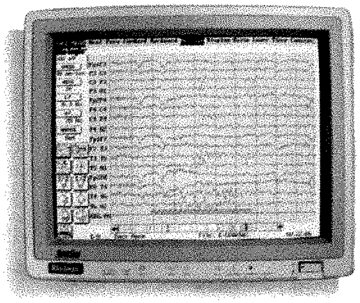

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Calendar of Meetings

September

16-20 Annual Meeting of the American Electroencephalographic Society, Fairmont Hotel, San Francisco, Calif. Contact Jacquelyn T. Coleman, Executive Director, American Electroencephalographic Society, PO Box 30, Bloomfield, CT 06002; (203) 243-3977.

October

2-3 The Meeting of Medical Traditions in New Spain, Los Angeles, Calif. Contact Susanne M. Kahle, Assistant to the Director, 1992 Quincentenary Programs, 212 Royce Hall, University of California, 405 Hilgard Ave, Los Angeles, CA 90024; (310) 206-1305.

5-6 Second International Congress on Objective Assessment in Rehabilitation Medicine, Montreal, Quebec. Contact Centre de Formation en Readaptation du Quebec, 6300 Ave Darlington, Montreal, Quebec, H3S 2J4 Canada; (514) 340-2089.

23-24 "Transcranial Doppler and Cerebral Blood Flow Monitoring: Applications in Neurology, Neurosurgery, and Anesthesiology," Sheraton Miramar Hotel. Contact UCLA Division of Neurosurgery, 10833 Le Conte Ave, Los Angeles, CA 90024; (310) 206-0626.

November

23-25 Fifth Course in Spanish of the American Academy of Neurology, Doral Hotel, Miami Beach, Fla. Contact Office of Continuing Education, State University of New York Health Science Center at Syracuse, 750 E Adams St, Syracuse, NY 13210; (315) 464-4606.

27-29 Third International Headache Research Seminar, Copenhagen, Denmark. Contact Mrs Vibe Halling, Third International Headache Research Seminar, Department of Neurology, Gentofte Hospital, Niels Andersens Vej 65, DK-2900 Hellerup, Copenhagen, Denmark.

Tinnitus: Diagnosis/Treatment

By Abraham Shulman, with Jean-Marie Aran, Harald Feldmann, Juergen Tonndorf, and Jack A. Vernon, 571 pp, $95, Philadelphia, Pa, Lea & Febiger, 1991.

This treatise on tinnitus, divided into five sections, presents a detailed history of tinnitus research, a thorough analysis of the mechanisms of tinnitus, a review and explication of a new diagnostic battery, evaluation of current and suggested new treatment procedures, and a perspective on the future. It is offered as an introductory text on the symptoms of tinnitus for use by professionals involved in the care of those who present subjective idiopathic tinnitus. The research and clinical findings reported should prove of great value to those involved in, or those contemplating, research on tinnitus. Additionally, those conducting training programs in otolaryngology, audiology, neurology, and psychology will find this textbook a valuable resource.

The extensive coverage begins with a detailed accounting of the precursors to modern day understanding of the phenomenon and carefully leads one through the basic science underlying tinnitus; early and current auditory system and tinnitus models; psychophysical and psychoacoustic correlates of tinnitus; electrophysiology of the auditory system; auditory brain-stem response measures; the efferent auditory system and its relationship to tinnitus; neurotransmitters; epidemiology; classification systems; medical evaluation; tinnitus evaluation; a medicoaudiological patient protocol and its application; types and origins; and treatment methods, including drug therapy, the place of surgery in treatment, instrumentation, and other forms of tinnitus treatment and control.

The principal authors and their colleagues have demonstrated originality in quantifying subjective idiopathic tinnitus. They concede the ubiquitous character of tinnitus in patients with sensorineural hearing impairment and confirm the hearing impairment through conventional and/or high-frequency audiometry. They view tinnitus as a symptom of neurotologic disease of the cochleovestibular system and propose that tinnitus arises within the system itself or may reflect other sensory disturbances that find their expression via the auditory system. The tinnitus model suggested by Shulman is based on the assumption that tinnitus is the subjective manifestation of a dysynchrony in the auditory system, either peripheral or central, and a model that recognizes the interplay of auditory afferent and efferent systems.

The authors emphasize the great variability that exists among individuals seeking professional help for subjective idiopathic tinnitus. It can arise anywhere in the cochleovestibular system, even in cerumen blockage of the external auditory canal or in cases of otitis media. Patients report it variously as a ringing, hissing, ocean roar, clicking, pounding, or cricket sound and as tones, noise, or both. Only during acute attacks of Meniere's disease is it apparently consistent, ie, as a low-pitched roaring sound. As to its localization, tinnitus is reported as unilateral, bilateral, inside the head, outside the head, in the back of the head, or any combinations of these.

Research and clinical observations by Shulman and his associates over nearly 10.5 years have enabled them to develop a system for diagnosing clinical types of subjective idiopathic tinnitus. Their medicoaudiolgic orientation to the problem is grounded on basic research of the cochleovestibular system, including psychophysics, psychoacoustics, electrophysiology, auditory neurophysiology, and neurotransmitters. Their *medical audiologic tinnitus patient protocol* consists of history, physical examination, cochleovestibular test battery, tinnitus evaluation, and a trial of instrumentation. The objectives for its application are to (1) objectively identify subjective idiopathic tinnitus; (2) establish a presumed site of lesion; (3) codify response patterns of the cochleovestibular system; and (4) integrate findings into a strategy for treatment.

Shulman and his associates recommend a medical examination that includes the following components: complete clinical history; general medical examination; general otolaryngological examination; neurotologic examination; cochleovestibular evaluation; and the tinnitus evaluation. Because the patients referred usually have serious problems, information is sent to them prior to their examination. The information packet describes the diagnostic approach and the goals of tinnitus control. The packet mentions that a cure is not known and describes the various approaches to control.

The medical examination is followed by the otolaryngologic and the neurotologic examinations. These, in turn, are followed with the administration of a specialized series of tests called the *electrodiagnostic cochleovestibular test battery*. This consists of auditory brain-stem response, the computerized rotary chair and pursuit tracking test, the electrical high-frequency audiometer, and impedance audiometry.

The tinnitus evaluation battery identifies and quantifies the subjective complaint of tinnitus. It is the task of the audiologist, and the findings are correlated with those of the neurotologist. The results of such procedures as pitch matching, loudness match, measurement of postmasking effect (sometimes referred to as *forward masking* or *residual inhibition*), Feldmann masking curves, and minimal masking levels result in medicoaudiologic results and enable the planning for tinnitus treatment and control.

The authors point out that treatment of a symptom usually implies a cure. In general, they speak of control but not cure. They caution that it is essential within the present state of the art to differentiate between treatment and control. They define *tinnitus control* as the methods and/or procedures that provide relief to the patient with tinnitus.

Instrumentation is reportedly the most reliable and safest method for providing relief to the patient with subjective idiopathic tinnitus. Hearing aids, first recommended as early as 1941, continue to be part of the tinnitus control option. More recently, Vernon has introduced the tinnitus masker as a wearable device for tinnitus control. The tinnitus masker, in effect, substitutes one sound for another, ie, an externally produced auditory sensation for the perceived tinnitus. The rationale, application, and results of these are presented in detail in chapters by Vernon and by Shulman. The less efficacious instrumentation mode is that utilizing electrical stimulation.

Drug therapy can play a significant role in tinnitus control strategies but is not recommended as a treatment of first choice. The authors draw attention to complications from drugs in general and to drug therapy. Those drugs most frequently associated with tinnitus are characterized under the following three headings: (1) drugs that elicit tinnitus; (2) drugs that relieve or suppress tinnitus; and (3) drugs that treat factors influencing tinnitus. Eliciting types generally are those that are ototoxic; the suppressing variety are random and not specific to tinnitus; the third category, the antianxiety type, relates to the affect side of subjective idiopathic tinnitus. Knowledge of the ototoxic drugs used in other treatment regimens has served as a preventive measure. Although no single drug therapy has yet been made available specifically for subjective idiopathic tinnitus, the future prospects are viewed as positive.

The authors point out that individuals, by virtue of genetic predispositions—whether drug sensitivities or variations in auditory thresholds—show different levels of tolerance for chemical compounds in pharmaceuticals and food substances. They cite the example of tinnitus secondary to ingestion of aspirin in patients afflicted by severe rheumatoid arthritis. In addition to those salicylates offered in therapeutic regimens—whether for rheumatoid arthritis or simple use for antipyrogenic, anti-inflammatory, or anticoagulant effect—naturally occurring salicylates are widely prevalent in food. Accordingly, it is not unreasonable to consider a subgroup of patients with tinnitus who exhibit an increased sensitivity to salicylates found in food and other ingestants. This does not exclude other dietary contributions to causes of tinnitus, such as hypoglycemia, hyperlipidemia, and the use of ethanol or caffeine. In general, evidence suggests that alcohol is an ototoxic substance resulting not only in tinnitus but in cochlear cell damage and sensory neural hearing loss in many patients.

Three types of patient groups are described: those who ignore their tinnitus; those who can cope with the problem; and a small group, estimated to be in the 5% range, who are driven to absolute distraction, some of whom may be suicidal. Therefore, psychological status needs to be evaluated for its significance as adjunct therapy in tinnitus treatment and control. With respect to surgical treatment, it is recognized that surgery for the underlying disease may influence the symptom of tinnitus: it may be increased, decreased, or remain unchanged. What is important is that tinnitus alone is not an indication of surgery.

The variability in individuals presenting tinnitus is sufficiently great to warrant combined methods of treatment and control. Prevention through nonuse or monitored use of ototoxic drugs in medical practice and control of damaging noise levels are more broadly recognized for their importance. Future breakthroughs in tinnitus prevention and treatment await further advances in the understanding of the basic underlying mechanisms of tinnitus.

Shulman and his colleagues in this country and abroad have raised the visibility of tinnitus as a significant problem. He strongly urges the study of tinnitus as a discipline, thus providing a structural framework for the integration of clinical otology with basic sciences. Further, they suggest that this new discipline be called *tinnitology*.

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Neuroreceptor Mechanisms in Brain: Advances in Experimental Medicine and Biology

Volume 287, edited by Shozo Kito, Tomio Segawa, and Richard W. Olsen, 498 pp, $115, New York, NY, Plenum Press, 1991.

This book is a collection of 42 papers presented at the Third International Symposium on Neurotransmitter Receptors held in Hiroshima, Japan, during February 1990. During the past few years, the field of neurotransmitter receptors in the brain has been progressing at an unprecedented pace. The topics covered in this book include structural and functional studies on some well-characterized receptor proteins and characterization of receptor-coupling mechanisms, receptor interactions, and receptor regulation, with the emphasis on the central nervous system. The receptors covered in these proceedings include tachykinin, inositol 1,4,5-triphosphate, serotonin, adrenergic, dopamine, nicotinic acetylcholine, muscarinic, GABA (γ-aminobutyric acid), and excitatory amino acid receptors. The multiple roles of neuropeptides such as tachykinin and calcitonin are also presented to illustrate the broad impact of neuropeptides. Phosphoinositide as a second messenger system and its receptor are discussed in a number of chapters.

Techniques described include molecular pharmacology, receptor solubilization and purification, imaging of second messengers in cells and intact brain, and the use of recombinant DNA technology. This book presents a good collection of the latest information available on a number of receptors and their second messenger systems. These proceedings will be valuable to the neuroscientists who want to be familiar with the current research in neuroreceptors and their mechanisms in the central nervous system.

JEAN M. BIDLACK, PHD
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LETTERS TO THE EDITOR

Binswanger's Disease and German Translations

To the Editor.—"It seems rather pointless to argue whether a given case represents Binswanger's disease without first describing what is meant by this term. We may also agree that it is fruitless to try to match one's own cases with the original publication of Binswanger since the latter does not contain sufficient details for such a comparison."[1]

One of the most important publications on this subject, that of Olszewski,[1] was not mentioned by the authors of the recent translation[2] of Binswanger's article. Although there have been several advances with computed tomography, magnetic resonance imaging, and correlative pathologic studies, Olszewski's fundamental contribution was a translation and analysis of the *relevant* portions of Binswanger's original article and a meticulous clinicopathologic correlation involving his own cases and those mentioned by Binswanger. Perhaps Olszewski's article was omitted by the authors on the assumption that it was adequately covered in some of their references. If so, such an assumption was a serious error in judgment. Simply reading some of the cited review articles, many of which are really compilations of articles, not critical reviews of them, will demonstrate this fact. The authors' translation of Binswanger's verbose article from what they refer to as "stilted" German unfortunately, and almost necessarily, emerged as "stilted" English. In their Commentary, the authors also inserted some references of dubious relevance (their references 20 and 21, one of which contains a misspelling [the editor's name was Owman, not Owmen]). The net effect of the translation and Commentary, however good the authors' intentions, was to perpetuate the notion that there is such a thing as "Binswanger's disease" sui generis. Their comments about "classic article" and "eponymic medical immortality" only add to the confusion.

As for Binswanger's "immortality," please check the *Founders of Neurology*.[3] The editors were Webb Haymaker, a neurologist-neuropathologist, and Francis Schiller, a distinguished historian of neurology; both were fluent in German, stilted and otherwise. Binswanger is mentioned in their authoritative biographic history only once in Berger's biography written by F. A. Gibbs and only because he was the predecessor of Hans Berger at Jena.

For the last word (all humorous, so relax) on German, stilted and otherwise, consult Mark Twain.[4] For a continuous display of stilted English, consult current medical journals.

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1. Olszewski J. Subcortical arteriosclerotic encephalopathy: review of the literature on the so-called Binswanger's disease and presentation of two cases. *World Neurol.* 1965;3:359-375.
2. Blass JP, Hoyer S, Nitsch R. A translation of Otto Binswanger's article 'The delineation of the generalized progressive paralyses.' *Arch Neurol.* 1991;48:961-972.
3. Haymaker W, Schiller F (eds). *Founders of Neurology*. 2nd ed. Springfield, Ill: Charles C Thomas Publisher; 1970:171.
4. Twain M. The awful German Language. In: Twain M; Neider C, ed. *A Tramp Abroad*. New York, NY: Perennial Library, Harper and Row; 1977.

In Reply.—We appreciate Moossy's interest in our translation of Binswanger's classic article.[1] With the growth of the medical literature, complete discussion of previous work within available space becomes more and more challenging. We did not mean to slight Olszewski's contribution in *World Neurology* in 1965. Medical historians of good will can differ about the magnitude of Binswanger's contribution. Many German neurologists consider him, together with Alzheimer, to have been one of the pioneers in delineating cerebrovascular diseases and distinguishing these diseases from other conditions, including neurosyphilis. Our complete translation meant to lay out some of Binswanger's insights that go beyond clinical and pathologic description and appear to relate to some of the current controversies about vascular dementias.

The German medical tradition of which Binswanger was a part emphasized the complexity of the relationship between tissue pathology and clinical symptomatology. Clearly, clinical signs and symptoms depend, in part, on the nature and extent and in the nervous system on the location of pathologic abnormalities. But the *clinical* abnormalities also depend, significantly, on the endowment the individual had to begin with and on what the individual is called on to do. The analogy has been drawn to damage to a road. The effects on traffic depend, in part, on where the road is, how busy it is, whether or not it is rush hour, and what alternate routes are available.

These factors have been recognized to be important in correlating pathologic to clinical abnormalities in Alzheimer's disease. Katzman and colleagues[2] have proposed that people who have the full neuropathologic picture of Alzheimer's disease at autopsy, although they functioned well during life, may have had a larger neurologic reserve. It is quite possible, although difficult to prove, that had these individuals lived longer, progression of the pathologic process would have led to clinical disability. It is also quite possible that detailed neuropsychologic testing would have identified abnormalities in them. Detailed neuropsychologic testing detects abnormalities in one of the writers of this letter, who was a dyslexic child. It is experimentally clear, however, that *the tissue pathology alone does not predict the clinical disability*.

Similar considerations apply to vascular dementias, and modern imaging techniques have made them more important. It is widely recognized that asymptomatic strokes can mark the presence of cerebrovascular disease, even though they are a "coincidental" finding without significant functional consequences for the affected patients under normal circumstances of life. Modern imaging techniques, and notably T_2-weighted magnetic resonance imaging, can detect alterations in people not yet at autopsy that correlate in at least some studies with the presence of vascular risk factors and neuropathologically with changes associated with vascular disease.[3,4] The radiologic changes are associated not only with vascular dementia but also, at lower prevalence, with other neuropsychiatric disorders, and they are found as well in a significant proportion of older people who have no clinically significant disability related to the brain.[5] One way to explain these data is that the findings by means of magnetic resonance imaging mark a pathophysiologic process that has a complex relationship to the clinical findings. We hypothesize that for subcortical vascular disease as for cortical, the clinical symptoms depend on the nature, extent, and location of the lesions; on each patient's original endowment; and on what the patient is asked to do. In preparing a study to test that hypothesis, specifically in relationship to damage to portions of the brain involved in the regulation of affect,[6] we reviewed the literature and found that Binswanger had put forward this view in his original articles in 1894. Therefore, we translated his articles in full.

Our translation attempted to give the reader a feeling for Binswanger's time and place, requiring formal language. *Tempus mutandis et nos mutandur illis.* The problem with language that is resolutely up to date is that it is soon enough out of date.

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1. Blass JP, Hoyer S, Nitsch R. A translation of Otto Binswanger's article 'The delineation of the generalized progressive paralyses.' *Arch Neurol.* 1991;48:961-972.
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4. Awad IA, Johnson PC, Speltzer RF, Hodak JA. Incidental subcortical lesions in the elderly, II: postmortem pathological correlations. *Stroke.* 1986;17:1090-1097.
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Wilson's Disease: Hypothesis of a Deficiency of Copper Excretion Via the Endosome to the Bile

To the Editor.—It has been shown that intravenously administered polymeric IgA in the rat is captured by a receptor in the liver parenchymal cells and transported via the endosomes to the bile canaliculus where it is excreted.[1]

We would like to suggest that a similar mechanism could be operating for the transport of a copper-protein to the human bile and that there is a genetic impairment of this pathway in Wilson's disease entailing insufficient copper excretion. As a consequence of the impaired pathway via the endosome, copper would be routed to the lysosome where it accumulates secondarily. The model would explain the insufficient excretion of copper in the bile[2,3] and the lysosomal engorgement in Wilson's disease.

The hypothesis of an endosomal route of copper to the bile canaliculus could probably be tested in laboratory animals by the administration of copper and another protein destined for lysosomal breakdown, both labeled differentially, and comparing the subsequent subcellular distribution of the radioelements in endosomes and lysosomes in liver cells.

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1. Courtoy PJ, Limet J, Quintart J, Schneider YJ, Vaerman JP, Baudhuin P. Transport of IgA into rat bile: ultrastructural demonstration. *Ann N Y Acad Sci.* 1983;409:799-802.
2. Gibbs K, Walshe JM. Biliary excretion of copper in Wilson's disease. *Lancet.* 1980;2:538-539.
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The National General Practice Study of Epilepsy

The Syndromic Classification of the International League Against Epilepsy Applied to Epilepsy in a General Population

Mark Manford, MRCP; Yvonne M. Hart, MRCP; Josemir W. A. S. Sander, MD; Simon D. Shorvon, FRCP

• In this prospective, population-based study of 594 cases of newly diagnosed epilepsy, proportions in categories as defined by the International League Against Epilepsy (ILAE) were as follows: (1) localization-related epilepsies: 1.1* idiopathic, 1.2%; 1.2* symptomatic, 16.2%; and 1.3 cryptogenic, 24.6%; (2) generalized epilepsies: 2.1* idiopathic (idiopathic generalized epilepsy) with 3-Hz spike and wave: absence epilepsy, 2.2%; juvenile myoclonic epilepsy, 1.5%; and nonspecific idiopathic generalized epilepsy, 5.6%; 2.3.1* symptomatic generalized epilepsies, 1.5%; 2.3.2* specific syndromes with generalized epilepsy, 0.3%; 3.2 seizures without unequivocal focal or generalized features, 32%; 4.1 situation-related syndromes, isolated seizures, 9.9%; seizures due to acute toxic or metabolic cause,* 4.5%. Only 33.6% were in diagnostic ILAE categories (asterisks) and many rare syndromes were not represented. The remainder (66.4%) were in various nonspecific categories. Only 24% of localization-related epilepsies could be clinically localized to a single ILAE-proposed site of origin and of these best localized cases, 14% had strongly discordant imaging or electroencephalograms. These major problems in applying the ILAE classification to epilepsy in the general population and its underemphasis of modern imaging techniques are discussed.

(*Arch Neurol.* 1992;49:801-808)

The recognition of shared and distinctive features of diseases remains a fundamental principle in their classification and is essential for coherent investigation. The International League Against Epilepsy (ILAE) proposed a basic division of epilepsies[1,2] that was refined recently[3] to include numerous, narrowly defined syndromes and several nonspecific categories into which all generalized and partial epileptic seizures should fall (Table 1). The idiopathic generalized epilepsies (IGE) are classified based on the age of onset and combination of seizure types. Partial seizures are attributed to restricted sites of the cerebral cortex, predominantly according to their clinical features (Table 2), with supportive evidence from electroencephalography (EEG), although it is acknowledged that many partial seizures occur in the absence of specific interictal, and sometimes also ictal, EEG change. The principles were established based on the literature, ictal telemetry recordings, and the experience of a panel of experts, all sources derived primarily from patients seen in referral centers. Patients attending these centers may represent a selected and atypical group; in particular, those referred for consideration of focal surgery may have more easily localizable seizures than patients elsewhere. If the model is to be meaningful in pathophysiologic and clinical terms, it should account for all seizures, not only those occurring in patients with severe disease, patients from tertiary referral centers, or refractory patients.

The National General Practice Study of Epilepsy (NGPSE) is a prospective, population-based incidence study, identifying patients at the time of first diagnosis, avoiding the potential bias of hospital-based studies.[4-6] By attempting to categorize these cases according to the ILAE classification, this study aims to do the following: to identify the proportion of epilepsy in the general population that falls into the clearly defined syndromes or the nonspecific categories of the ILAE; to estimate the relative incidence of different ILAE syndromes; to assess the clinical criteria of the ILAE for anatomic localization of localization-related epilepsies; to identify cases with discordance of localization by clinical, EEG, and imaging methods; and to review the criteria for defining epileptic syndromes. In addition to discussing epileptic syndromes, patients are also categorized by seizure type, as defined by the ILAE,[2] and by seizure etiology.

METHODS

Details of the methods of the study have been described elsewhere.[4-6] In summary, 275 general practitioners notified the study of all patients older than 1 month old in whom a new diagnosis of definite or possible epileptic seizures was made during a 3-year prospective recruitment phase. The practices were located around the country in urban and rural areas to avoid demographic sources of bias. Patients were followed up by the study at 6 months and then at yearly intervals; to date, follow-up is from 4 to 7 years. Details of hospital and specialist assessment and results of investigations were also obtained. The study population is thus an unselected cohort of patients with newly diagnosed epilepsy, identified at general population level, in whom com-

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Accepted for publication April 6, 1992.

From the Chalfont Centre for Epilepsy, Buckinghamshire, England.

Reprint requests to Chalfont Centre for Epilepsy, Chalfont St Peter, Gerrards Cross, Buckinghamshire, England SL9 ORJ (Dr Manford).

Table 1.—Patients Grouped According to the International League Against Epilepsy Classification of Epileptic Syndromes[2]

		No. of Cases (%)
1	Localization-related epilepsies	252 (31)
1.1	Idiopathic (with age-related onset)	
	Benign childhood epilepsy with centrotemporal spikes	7 (0.9)
	Childhood epilepsy with occipital paroxysms	0 (0)
	Primary reading epilepsy	0 (0)
1.2	Symptomatic	96 (11.8)
	Chronic progressive epilepsia partialis continua of childhood	0 (0)
	Syndromes characterized by seizures with specific modes of precipitation	0 (0)
	Temporal, frontal, parietal, and occipital lobe epilepsies	96 (11.8)
1.3	Cryptogenic	
	Temporal, frontal, parietal, and occipital lobe epilepsies	146 (17.9)
2	Generalized epilepsies and syndromes	66 (8.1)
2.1	Idiopathic (with age-related onset)	55 (6.8)
	Benign myoclonic epilepsy in infancy	0 (0)
	Childhood absence epilepsy/juvenile absence epilepsy*	13 (1.6)
	Juvenile myoclonic epilepsy (impulsive petit mal)	9 (1.1)
	Epilepsy with generalized tonic-clonic seizures on awakening	0 (0)
	Syndromes characterized by seizures with specific modes of precipitation	0 (0)
	Other idiopathic generalized epilepsies	33 (4.1)
2.2	Cryptogenic or symptomatic (in order of age)	0 (0)
	West syndrome (infantile spasms)	0 (0)
	Lennox-Gastaut syndrome	0 (0)
	Epilepsy with myoclonic astatic seizures	0 (0)
	Epilepsy with myoclonic absences	0 (0)
2.3	Symptomatic	11 (1.4)
2.3.1	Nonspecific etiology	0 (0)
	Early myoclonic encephalopathy	0 (0)
	Early infantile epileptic encephalopathy with suppression burst	0 (0)
	Other symptomatic generalized epilepsies	9 (1.1)
2.3.2	Epilepsies due to specific neurologic diseases	2 (0.2)
3	Epilepsies undetermined whether focal or generalized	190 (23.3)
3.1	With both generalized and focal seizures	0 (0)
	Severe myoclonic epilepsy in infancy	0 (0)
	Epilepsy with continuous spike waves during slow wave sleep	0 (0)
	Acquired epileptic aphasia (Landau-Kleffner syndrome)	0 (0)
	Other undetermined epilepsies	0 (0)
3.2	Without unequivocal focal or generalized features	190 (23.3)
4	Special syndromes	306 (37.6)
4.1	Situation-related epilepsies	
	Febrile convulsions	220 (27.0)
	Isolated seizures or status epilepticus	59 (7.2)
	Seizures due to an acute toxic or metabolic event	27 (3.3)
Total		**814 (100)**

*Classified separately in the International League Against Epilepsy classification. Seizures occurring before 1 month of age were excluded from the National General Practice Study of Epilepsy, including benign neonatal convulsions (category 2.1), benign neonatal familial convulsions (category 2.1), and neonatal seizures (category 3.1).

prehensive clinical details have been obtained. Considerable emphasis in the design of the study was placed on avoiding sources of selection bias in the identification of the study group and in obtaining comprehensive clinical data from primary and secondary care sources; the study has been uniquely successful in these regards. We believe, therefore, that the study group is truly representative of newly diagnosed epilepsy as it occurs in a general population.

A total of 1195 patients were notified to be in the study and were classified by the study panel.[5] Of these, 104 were excluded because of previously diagnosed epilepsy or neonatal seizures. Seventy-nine cases were diagnosed as nonepileptic seizure disorders, mostly syncope or psychogenic attacks, and a further 198 cases of possible, but not definite epilepsy, are excluded from this analysis. Two hundred twenty had febrile seizures and the remaining 594 patients were classified as having definite epileptic seizures. This represents a small increase in the number of definite cases of epilepsy in the NGPSE since previous reports,[5,6] because of reclassification of some previously uncertain cases, in the light of new data. Patients' characteristics are given in more detail by Sander et al.[5] These 814 patients were categorized according to the ILAE classification of epileptic syndromes,[3] applying criteria summarized in Table 3. Localization-related seizure origin was classified as conforming to a single ILAE category, a region constituting two or more neighboring ILAE categories, as lateralizable, or as unlocalizable within the ILAE classification (Table 2). Patients were also categorized by seizure type according to the ILAE classification[2] and by seizure etiology.

Etiologic factors were classed as definitely significant, eg, glioma, or probably significant, eg, moderate perinatal trauma. Vascular disease was accepted only as definitely significant where there was a clear history of central nervous system vascular

Table 2.—Summary of the International League Against Epilepsy Classification of Localization-Related Seizure Manifestations[2]

Cortical Region	Clinical Seizure Pattern
Supplementary motor	Postural, simple focal tonic with vocalization, speech arrest, fencing, and complex focal with urinary incontinence
Cingulate	Complex focal with initial automatisms with sexual features, vegetative signs, changes in mood and affect, and urinary incontinence
Frontopolar	Initial loss of contact, adversive and subsequent contraversive movements of head and eyes, axial clonic jerks, falls, and autonomic signs with frequent generalized tonoclonic seizures
Orbitofrontal	Complex focal with initial automatisms or olfactory hallucinations, autonomic signs, and urination
Dorsolateral (premotor cortex)	Simple focal tonic with versive movements and aphasia and complex focal with initial automatisms
Opercular	Mastication, salivation, swallowing, and speech arrest with epigastric aura, fear, and autonomic phenomena; partial clonic facial seizures may be ipsilateral and gustatory hallucination is common
Primary motor	Contralateral tonoclonic movements according to somatotopy, speech arrest, and swallowing with frequent generalization; ipsilateral leg involved in paracentral seizures
Mesial temporal	Autonomic or psychic phenomena with gustatory or olfactory sensations and epigastric sensations; in complex partial seizures; speech and motor arrest with oroalimentary automatism
Lateral temporal	As mesial temporal with additional somatosensory, visual, or auditory manifestations
Parietal	Somatosensory manifestations and loss of muscle tone, with intra-abdominal sensations; visual manifestations are often formed hallucinations; sometimes negative sensory phenomena
Occipital	Visual hallucinations, formed or unformed, with eye and head movements and distorted visual perception

events—stroke or transient ischemic attack—or evidence of cerebrovascular disease on neuroradiologic imaging. Extracranial vascular diseases, eg, myocardial infarction, were considered probable or possible indicators of cerebrovascular disease (see Sander et al[5]).

RESULTS

Classification of Epileptic Syndromes (Table 1)

Localization-Related Epilepsies (Categories 1.1, 1.2, and 1.3).—Two hundred forty-five patients experienced epilepsy that was localization related based on clinical features or EEG findings. Of these, 14 had strong EEG evidence of partial onset without any focal clinical clues; in 10 the EEG showed temporal spikes. An additional seven patients were included in this category who had generalized seizures with no historical clues and an unremarkable EEG but focal abnormalities on computed tomographic (CT) scan.

Benign epilepsy with centrotemporal spikes (BECT) was strongly suspected in seven children based on electroclinical features, although not all had undergone sleep studies or neuroimaging. No other idiopathic, partial epilepsies were identified. A cause was identified in 39.2% of the other 245 cases of localization-related epilepsies.

Generalized Epilepsies (Category 2.1).—In 41 patients, a diagnosis of IGE, with 3-Hz spike and wave, could be made based on a typical appearance of the EEG, associated with generalized seizures (Table 4). In only 19 of these was there a cluster of seizure types that allowed a syndromic classification to be made. A further three patients had a clinical picture suggestive of juvenile myoclonic epilepsy, but EEG data were absent or nonspecific. One girl, aged 4 years, had absence seizures with an EEG suggesting but not diagnostic of IGE, and 10 patients had tonoclonic seizures, with an EEG suggesting a generalized epilepsy, without the classic 3-Hz appearance. The remaining 22 patients had a typical 3-Hz EEG appearance but experienced only tonoclonic seizures, with no particular diurnal pattern; in five of these patients there was only a single seizure during the follow-up period.

Of 13 patients with absence epilepsy, 10 (77%) were female. Other types were nearly evenly distributed between the sexes.

The age of onset of absence epilepsy ranged from 4 to 15 years and was significantly younger than the onset of IGE without absences ($P<.001$, Wilcoxon Rank-Sum test). The patient numbers were small but there was no evidence of a bimodal age distribution, as suggested in the ILAE classification scheme. Onset of EEG definite IGE, not falling into an ILAE syndrome, was from the age of 8 to 45 years (median, 15 years), with only two patients older than 20 years. Clinical presentation was between the ages of 14 and 20 years in all nine patients with myoclonic epilepsy, which was not significantly different from other types of IGE, excluding those with absence attacks.

Categories 2.2, 2.3, and 3.1.—No patient was identified in categories 2.2 or 3.1 of the ILAE classification. To confirm this finding, we focused on all patients younger than 8 years presenting with more than one seizure type or frequent seizures. We found 11 cases in which the electroclinical pattern pointed to a possible diffuse epilepsy, with combinations of, eg, absence, akinetic, tonoclonic, and myoclonic seizures, in 10 children associated with mental handicap. In two cases there was a specific disease process: Batten disease and neuroaxonal dystrophy (classified as 2.3.2) and in eight others there were various factors thought to be causative in their perinatal or infant history (classified as 2.3.1). However, on the data available, it was not possible to assign them to specific syndromes. There were, for example, no cases of Salaam attacks or hypsarrhythmia to suggest West's syndrome and none with slow spike and wave on EEG, consistent with Lennox-Gastaut syndrome.

Epilepsies Undetermined Whether Localization Related or Generalized (Category 3.2).—In 107 patients, the epilepsy could not be classified as generalized or localization related based on clinical features or EEG, although

Table 3.—Criteria for Inclusion in International League Against Epilepsy (ILAE) Categories

Types of Epilepsy

1) Localization-Related Epilepsies
  1.1) Idiopathic: children of appropriate age with typical electroclinical features of these relatively well-defined syndromes and no evidence of alternative etiology
  1.2) Symptomatic: patients with recurrent seizures with clinical or electrophysiologic evidence of focal onset and historical or imaging evidence of causation; electroencephalographic (EEG) criteria were focal sharp waves or spikes; slow-wave abnormalities were not accepted unless consistently focal
  1.3) Cryptogenic: patients with recurrent seizures with clinical or EEG evidence of focal onset, but no evidence of causation

For the purpose of analysis, conformity of partial seizure features to sites of onset proposed by the ILAE (Table 4), was classified as below.
  1) Localized to site: patients whose seizure symptomatology fit only into a single ILAE category, with no incongruous symptomatologic features
  2) Localized to region: patients whose seizure manifestations overlapped at least two, frequently more, neighboring ILAE categories
  3) Lateralized: patients with seizures that could be clinically localized to one hemisphere but no further sublocalization was possible
  4) Unlocalized: patients whose seizures suggested a partial onset that could not be localized

2) Generalized epilepsies
  2.1) Idiopathic generalized epilepsies (IGE); neonatal convulsions were excluded in the study design and to facilitate analysis, the following categories were identified:
    a) Definite IGE: patients with clinically generalized seizures and characteristic EEG changes of 3-Hz spike and wave activity or a photoparoxysmal response; the clinical characteristics were analyzed to assess whether they fell into one of the syndromes defined by the ILAE
    b) EEG probable IGE: generalized abnormalities suggestive but not typical of IGE, eg, atypical generalized spike and wave discharges, with clinically generalized seizures
    c) Clinically probable IGE: patients with a typical history of absence or myoclonic jerks but EEG unavailable or nonspecific
  2.2) Cryptogenic or symptomatic generalized epilepsies; patients displaying typical (usually multiple) seizure types of these specific syndromes, with characteristic associated EEG change, for instance Salaam attacks and hypsarrhythmia of West syndrome
  2.3.1) Symptomatic generalized epilepsies (excluding early myoclonic encephalopathy or early infantile epileptic encephalopathy with suppression burst); children of appropriate age with several generalized seizure types and characteristic EEG changes, eg, tonic seizures with slow spike and wave in Lennox-Gastaut syndrome
  2.3.2) Disease related; generalized seizures occurring in the context of specific diseases with recognized neurologic involvement

3) Epilepsies undetermined whether focal or generalized
  3.1) With both focal and generalized seizures; patients with typical electroclinical patterns of these syndromes, for instance, atypical absences, partial and generalized seizures, with diffuse spike and wave during slow-wave sleep
  3.2) Without focal or generalized features; generalized seizures, without unequivocal clinical or EEG features of generalized or focal epilepsy; in some cases, no EEG had been performed; these patients were subdivided into symptomatic or cryptogenic according to whether a cause could be identified

4.1) Special syndromes: situation-related epilepsies
  a) Febrile convulsions: less than six episodes occurring between the ages of 6 months and 5 years, all clearly associated with fever
  b) Acute symptomatic: generalized seizures occurring only in the context of an identified, acute medical illness
  c) Single generalized seizures (after at least 2 years' follow-up) with no obvious precipitant

Table 4.—Idiopathic Generalized Epilepsy (IGE) With 3-Hz Spike and Wave*

IGE	No.
Definite IGE with a specific ILAE syndrome	19
Definite IGE in nonspecific category	22
Clinically probable absence epilepsy	1
Clinically probable juvenile myoclonic epilepsy	3
EEG probable IGE, tonoclonic seizures only	10

*ILAE indicates International League Against Epilepsy; EEG, electroencephalogram.

Table 5.—Single Seizure Types

Seizure Type	No.
Acute symptomatic generalized	27
Remote symptomatic generalized	19
Generalized, cause unknown	40
Partial seizures	5
Idiopathic generalized with 3-Hz spike and wave	5

clinical history suggested a cause in 18 of these. In a further 83 patients, in 48 of whom a specific cause was suspected, the epilepsy was clinically unlocalized but there were no EEG data.

Special Syndromes: Situation-Related Seizures (Category 4.1).—Febrile convulsions were common, occurring in 27% of all patients. Single, acute symptomatic epileptic seizures were all generalized in clinical pattern but 13 of the 27 showed evidence of focal cerebral abnormalities (Table 5). In five others of the 96, the EEG showed 3-Hz spike and wave and in five more, seizures were partial in type. Partial seizures and IGE were much less likely to be isolated.

Localization of Partial Epilepsies

In 142 patients with simple and complex partial seizures and in 18 patients with secondarily generalized seizures, there was a sufficiently characteristic clinical onset to attempt seizure localization (Table 6).

In 27 patients, the clinical seizure pattern was sufficiently distinctive to allow it to be localized to a single ILAE category and in a further 22 patients, localization

Table 6.—Proposed Sites of Partial Seizure Onset of Localization-Related Epilepsies*

	No.
1) Localized to a single ILAE site	50
Motor cortex	31
Supplementary motor	6
Lateral temporal	3
Parietal	10
2) Overlapping neighboring ILAE regions	110
Frontal	30
Central	21
Frontotemporal	9
Temporal	40
Posterior cortex	10
3) Lateralized only	3
4) Unlocalized	92

*ILAE indicates International League Against Epilepsy.

to a single ILAE category seemed likely, although not all the features were congruent. The most readily identifiable were motor cortex (31 cases) and parietal cortex (10 cases), with jacksonian-type pure motor or pure sensory progression, respectively. Supplementary motor seizures were identified in six cases, although in this group laterality is more difficult to determine. In three cases the seizure appeared to be lateral temporal, according to the ILAE classification, on the basis of prominent sensory features, although it is difficult to exclude spread from mesial temporal structures.

In 110 cases the seizure could be localized to a region of cerebral cortex but had clinical features that overlapped two or more ILAE categories. Perirolandic seizures were seen in 21 cases, with varying emphasis between sensory and motor features that precluded their allocation to one or other region. Seizures with temporal lobe features were often difficult to attribute to either mesial or lateral temporal regions (40 cases). Ten cases had multimodal sensory features or a mixture of formed and unformed visual hallucinations preventing localization beyond the parieto-temporo-occipital cortices. In 30 cases the seizure pattern suggested frontal onset, anterior to the primary motor cortex, with prominent motor activity, including clonic, tonic, and automatisms, often combined with autonomic features, creating such diverse manifestations that the seizures could not be localized further. In nine cases the seizure overlapped frontal and temporal features.

In three cases the seizure was clinically lateralized, consistent with the side of a previous cerebral insult, but it could not be localized within the hemisphere.

In 44 patients there were clinical features to suggest a partial onset but these were nonspecific and inadequate to be of value in localization, eg, epigastric sensations, vague body sensations, autonomic phenomena, or head turning that are manifestations of numerous cortical areas. In 48 cases, the seizure was clinically generalized from the outset, although it was localization related on other historical or investigative evidence.

Discordant Cases

The evidence used to localize epilepsies was primarily clinical, in accordance with the ILAE classification (Table 7). In eight cases of partial epilepsy, the clinical classification pointed to a single region of seizure onset, but the CT scan demonstrated a significant lesion at a remote site. In one case there was a hemifield visual aura but the CT lesion was ipsilateral to the affected field. In a further four cases, the EEG showed focal features clearly remote from the site suggested by the clinical seizure manifestations and in one case of jacksonian sensory progression, it was lateralized opposite to the CT and clinical localization. Therefore, of 160 cases in which a clinical localization of partial seizure onset could be estimated, 13 (8.1%) had strongly discordant results of investigations and of these, seven were in the "clinically localized to site" group, representing 14% of all those clinically localized to a single ILAE site.

Seizure Types

Of 594 patients with definite epilepsy, 504 (85%) experienced one seizure type, 83 (14%) experienced two distinct seizure types, and seven (1%) suffered three or more.

Partial Seizures.—In 184 patients (49% female), there was clinical evidence of partial seizures, 56 of whom also suffered secondarily generalized seizures. Thirty-eight suffered simple partial seizures, of whom five also had complex partial attacks (complex partial seizures) and 16 also had secondarily generalized seizures. One hundred forty-six patients suffered complex partial seizures, of whom 38 also had secondarily generalized seizures.

Generalized Seizures.—Four hundred sixty-three patients (78%) experienced generalized seizures (including secondarily generalized seizures), of which 414 were tonic-clonic in type; 17 were myoclonic; 17 were nonfocal tonic; three were akinetic; and 29 were absences with no focal clinical features.

Etiology

If patients with single seizures, febrile seizures, and genetically determined epilepsies are excluded, the proportion of the remaining 533 patients in whom a cause could be identified on historical or imaging evidence (symptomatic cases) was 40% (Table 8). Of the 184 patients with partial seizures, with or without secondary generalization, a cause was identified in 39% compared with 41% in the 349 patients with only generalized seizures. The mean age of patients presenting with symptomatic epilepsy was 48 years and for those in the cryptogenic group it was 29 years. The proportions of male subjects in the two groups were 51% and 52%, respectively.

The most common partial seizures were hemiclonic attacks (52 cases) with or without secondary generalization. Seven patients had BECT and cerebrovascular disease was common in the remainder; nine were definite and five were probable cases. The chance of an identified etiology in temporal lobe seizures was only 14% compared with 51% for the other focal seizure types combined.

Gliomas were diagnosed more in partial than generalized seizures, whereas alcohol—either acute or chronic intoxication—was identified as the likely cause only in patients with generalized seizures. Other identifiable etiologic factors manifested frequently as both partial and generalized seizures.

COMMENT

The ILAE classification is based on the specialized experience of tertiary referral centers whose patients are highly selected and may not be representative of the broad base of epilepsy in the general population. To our knowledge, this is the largest population-based, prospective study of

Table 7.—Cases With Discordant CT and EEG*

Syndromic/Clinical Localization	EEG Localization	CT Localization	Etiology
	Clinically Localized to a Single ILAE Site		
Supplementary motor area	Anterior temporal	Not available	Unknown
Motor cortex	Temporal	Parietal	Glioma
R motor cortex	L frontotemporal	Normal	Unknown
Parietal	Normal	Frontal	Glioma
Anterior frontopolar	Temporal	Temporal	Infarction
L parietal	R parietal	L parietal	Glioma
Lateral temporal	Temporal	Frontal	Glioma
	Attributable to a Group of ILAE Sites		
Frontotemporal	Normal	Occipital	Unknown
Opercular	Temporal	Normal	Unknown
Opercular	Not available	Parietotemporal	Glioma
Temporal	Normal	Mesial frontal	Glioma
Orbitofrontal	Unlocalized	Occipital	Metastasis
L temporo-occipital	R temporal	R temporal	CT low density

*CT indicates computed tomography; EEG, electroencephalography; and ILAE, International League Against Epilepsy.

Table 8.—Etiologic Factors in Generalized and Partial Seizures

	Etiologic Factor			
	Definitely Significant		Probably Significant	
	Generalized Seizures	Partial Seizures	Generalized Seizures	Partial Seizures
Congenital disease	5	5	5	0
Birth trauma	1	1	2	0
Meningitis	1	0	0	1
Infarction	16	15	1	1
Vascular disease	7	5	20	10
Glioma	3	10	0	0
Meningioma	1	1	0	0
Metastases	5	4	2	1
Space-occupying lesion, uncertain type	4	3	0	0
Acute trauma	2	2	1	0
Remote trauma	0	0	4	3
Acute alcohol ingestion	3	0	3	0
Remote alcohol ingestion	4	0	20	0
Encephalitis	0	1	2	1
Other	8	7	22	2

epilepsy classification to date and, therefore, it is especially well placed to explore these issues. Its design would be expected to confer a different emphasis from previous studies that have relied on retrospective diagnosis from EEG or specialist records, or if prospective, have been hospital-based. Some cases were not referred to the hospital, eg, patients with known cerebrovascular disease or children with isolated seizures and others, though referred, never attended or attended nonneurologic clinics (eg, pediatric, psychiatric, or general medical). These patients would not be detected in a study based in a neurology unit. Three large studies have previously addressed the epidemiology of epilepsy in relation to the ILAE classification in broad terms, all using case ascertainment through hospital records but not evaluating partial seizure subtypes, according to the most recent ILAE classification.[7-9] Only one of these was an incidence study.[7]

Our results illustrate the rarity, in a general population, of many of the syndromes and categories described by the ILAE. Of the idiopathic, localization-related epilepsies (category 1.1), only BECT was identified—in 1.2% of epilepsies. No patient was identified in major categories 2.2 or 3.1 of the ILAE classification and only eight of the other 17 subdivisions were represented. Our analysis of all patients younger than 8 years, presenting with more than one seizure type or very frequent seizures, found 11 cases in which the electroclinical pattern pointed to a possible diffuse epilepsy, but none could be allocated to West syndrome or Lennox-Gastaut syndrome, two of the most common diagnoses in these categories in hospital-based series.[7-9]

Of the 594 patients with definite epilepsy, 66.4% of patients fell into groups 1.3, 3.2, or 4.1 (isolated seizures), "nonspecific categories," all of which are essentially vague and denote an inability to define the epilepsy in any detail, similar figures to those of Loiseau et al[7] who found they could classify 97% of seizures, including 38% of patients in nonspecific categories. A large proportion of epilepsy, therefore, remains indeterminate on current classification. The presence of nonspecific categories in the ILAE classification enables the categorization of virtually all patients, but it gives the false impression of diagnostic precision to what are essentially uncertain cases. In reality these categories do not help understanding of epilepsies in the general population, they do not provide information in relation to pathophysiology, and they do not identify internally homogeneous or mutually exclusive groups.

Localization-related epileptic syndromes were identified in 42.4% of cases compared with 28% by Loiseau et al.[7] We identified seven (1.2%) cases of BECT and no other idiopathic syndromes. Loiseau et al,[7] in a prevalence study of patients attending specialist clinics, found 5.4% of cases of BECT and a total of 6.9% of idiopathic syndromes and in a previous incidence study,[8] they found 2.0% with BECT and a total of 2.4% with idiopathic localization-related epilepsies.

Partial seizures occurred in 31% of patients compared with 15% to 38% in other studies.[7-15] We classified partial seizure localization according to the ILAE classification. In only 50 patients (27%) with focal onset partial seizures was the clinical picture sufficiently specific to be attributable only to a single ILAE site, although in a further 110 (60%), applying the ILAE criteria could narrow the seizure down to a general region. Certain clinical features have a well-defined anatomic correlate, ascribed to a single cortical region, eg, jacksonian motor progression, and therefore, they have high localizing power. Consequently, it was these seizure types that could be localized most accurately. Other manifestations are shared among several sites in the ILAE definitions and clinical seizure localization becomes an imprecise estimation of probabilities. Even in the "localized to site" group, there were seven (14%) in whom investigations were strongly discordant, of whom four showed clear structural lesions at remote sites on CT scan. It is instructive to consider these cases in some detail (Table 7). They represent seizure manifestations attributable to sites that have close intercortical connections with the location of the visible lesion: frontotemporal (uncinate fasciculus), frontoparietal (close somatotopy), and occipitofrontal (occipito-frontal fibers).

Similarly, the seizures attributable to a region were frequently types associated with a neuronal pathway constituting regions aggregated into a functional system. For example, although many seizures appeared to have exclusively hemisensory or hemiclonic manifestations, others had both features and were best classified as central sensorimotor. This is in accordance with physiologic evidence suggesting close relationships between the prerolandic and postrolandic regions.[16] Some seizures with prominent autonomic phenomena, often associated with visceral sensations, were attributable to various regions involved in the mesiolimbic system, but they were without features that could narrow them down further. Other seizures had polymodal sensory manifestations that are best described as "posterior," as they could arise from temporal or posterior parietal regions or spread into them from the occipital cortex and they cannot be attributed to one lobe. The presence of sensory manifestations in classical temporal lobe seizures points to lateral temporal involvement, either primary or secondary, but their absence does not necessarily mean a mesial temporal source and this group cannot confidently be categorized further on clinical grounds alone. Even those with sensory manifestations are frequently due to spread from mesial temporal structures.[17] The ILAE classification[3] attempts to localize seizures within the classical macroscopic cortical regions, whereas the functional systems that may mediate seizure spread overlap these divisions.

Loiseau et al[7] attribute seizures to larger cerebral regions rather than attempt to define very precise "foci" and our data support this general approach as more easily applicable in the general population. More precision may be appropriate to the presurgical evaluation of a minority of patients with very frequent localization-related seizures. Thus, we conclude that the ILAE classification scheme for localization is both not feasible in the great majority of cases of partial seizures and of uncertain relevance to partial seizure pathophysiology.

The proportion of patients with generalized epilepsies, excluding isolated and situation-related seizures, was 11.1%. Other epidemiologic studies have yielded proportions of 8.9% to 37.7%, with the higher figures obtained in studies from patients referred to specialist centers,[7-9] and they likely reflect referral bias. Loiseau et al[8] used a cross-sectional, hospital-based study design that gave a relative frequency of IGE of 8.5% compared with 7.4% in our own study. Their subgroups (our figures in parentheses) were as follows: absence, 23% (27%); juvenile myoclonic epilepsy, 11% (14%); and generalized tonic-clonic seizures, 63% (59%). Their more recent study[7] includes patients selected from highly specialized units and gives correspondingly higher figures, as did Gastaut et al[9] whose sample was age weighted, such that 50% of patients were younger than 16 years. Where subtypes have been addressed,[8-15] other epidemiologic studies give the relative incidence of juvenile myoclonic epilepsy as 0.9% to 2.2% (1.5%) and of absence epilepsy as 1.8% to 4% (2%).

Therefore, our figures for IGE are in accordance with other studies of this relatively well-defined subgroup, but in common with other studies, we found a substantial proportion of patients with a typical appearance of the EEG but only tonic-clonic seizures, which did not fall into any of the clear-cut categories of the ILAE. While it is recognized that patients may present with only tonic-clonic seizures before the complete syndrome emerges, our prospective follow-up of 3 to 7 years makes this unlikely to be a major factor. The ILAE classification also identifies pyknolepsy and juvenile absence epilepsy as separate syndromes. Although numbers are small, our data suggest that absence epilepsy is a condition that usually begins before the age of 15 years, but with no evidence of a bimodal onset. This is supported by the data from Gastaut et al[9] who found 85% of patients with typical absences presented to the hospital before the age of 16 years; many were probably even younger at the time of their first seizure, especially as this condition may remain undiagnosed for a considerable period. Tonic-clonic seizures occurred with absences in both the youngest and the oldest patients in our study. These findings suggest a continuum with age and do not support the ILAE subdivision into pyknolepsy and juvenile absence epilepsy.

Many studies have either looked at first seizures alone, assessing risk of recurrence, or else they have excluded single seizures from an epidemiologic study of epilepsy. Few have looked at both in the same study. The proportion of single seizures depends on the method of case ascertainment and it is to be expected that a community-based study will represent more accurately the incidence of single seizures as not every patient is referred to the hospital. Our study gave a proportion of 16% of single seizures compared with 10.8% of 1870 cases found by Juul-Jensen and Foldspang[15] and 9% by Loiseau et al.[7] The low single to multiple seizure ratio argues against single seizures being classified separately and the concept that multiple seizures are epilepsy but single seizures are not is difficult to explain in pathophysiologic terms. We support application of the concept of pre-epilepsy to patients who either have very rare seizures or in whom active epilepsy only lasts for a short time. These individuals, who will possibly never develop chronic epilepsy, in fact form the majority of those who suffer seizures in the general population.

The frequency of an identifiable seizure etiology was similar whether there was clinical evidence of partial seizure onset (39% partial vs 41% generalized). Of the identified causes, alcohol and congenital disease may be expected to induce a truly generalized epilepsy, but other acquired causes, eg, vascular disease or trauma, are focal cerebral insults. These abnormalities should be considered to cause localization-related epilepsies, even though they may frequently manifest with secondarily generalized seizures, with no focal seizure manifestations or interictal EEG clues to their focal onset. These findings highlight potential inconsistencies in the ILAE classification primarily by electroclinical features and argue for its rationalization, with more emphasis on epilepsy etiology as a major determinant of seizure mechanism.

The ILAE classification relies on clinical seizure patterns with support from EEG and is a development of a classification devised before modern imaging techniques became available.[18] Positron emission tomography is discussed in the classification in relation to temporal lobe epilepsy, but nowhere is specific reference given to CT or magnetic resonance imaging, despite the fact that these are widely available and useful investigations. Our patients with focal lesions on CT scan but no clinical or EEG evidence of partial epilepsy were best allocated to category 1.2 and represent some of the most clearly defined cases. Imaging is a major tool in the investigation of epilepsy and we believe it should be incorporated more fully into its classification. Epilepsy is a symptom and its syndromic classification by definition is imprecise, representing organized ignorance, whose aim is a provision of a framework for the elucidation of etiology and pathophysiology. Imaging is the most useful diagnostic test of etiology, and increasingly sensitive magnetic resonance imaging is now able to identify hitherto undetectable etiologies, eg, mesial temporal sclerosis or neuronal migration defects.[19,20] Imaging may also enable a generalized seizure of uncertain type to be redefined as localization related. Finally, where imaging and electrophysiology conflict in the identification of the region of seizure onset, there is increasing evidence that imaging may be the more reliable modality in certain situations.[21] It is important to recognize cases in which there is dissociation of results from different investigative modalities, as they may potentially give valuable information regarding mechanisms of epileptogenesis and seizure spread; a classification of the epilepsies should take this into account. We believe there is a necessity for frequent review of the classification in the light of new developments for it to retain its clinical and research value.

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Neurophysiological Basis of Cognitive Deficits in Long-term Survivors of Childhood Cancer

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• Thirty-three survivors of childhood cancer were tested with event-related potentials (P300), motor reaction time tests, and neuropsychological tests to assess the underlying physiological basis of treatment-related cognitive sequelae. Thirteen patients had received intrathecal chemotherapy, 11 had received intrathecal chemotherapy plus cranial radiotherapy, and nine had been treated without any form of central nervous system therapy. Neuropsychological performance of the groups treated without cranial radiotherapy was normal, but the group given cranial radiotherapy was significantly impaired. Mean reaction time and P300 latency were somewhat slower in the group given intrathecal chemotherapy relative to the group given no central nervous system treatment, but were significantly delayed in the group given cranial radiotherapy. Correlations of reaction time and P300 latency with neuropsychological test scores were also obtained. Results suggest that slowing of cortical activity secondary to white-matter damage may underlie cognitive decline in children treated with intensive central nervous system therapies, especially cranial radiotherapy.

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Significant advances in the treatment of childhood cancer have resulted in projected survival rates of 80% for children diagnosed in 1990, and the number of survivors in the United States by the year 2000 is projected to be about 200 000.[1] Much of the improvement in survival rates can be attributed to the use of prophylactic treatment to prevent infiltration of disease into the central nervous system (CNS),[2] to the development of new chemotherapeutic agents, and to the use of multidrug regimens. The ultimate goal of cancer therapy is patient survival, but medical survival is not always without cost to the patient. During the 1980s, greater emphasis was placed on the development of new therapies that minimize acute and late adverse effects yet provide medically effective treatment.[3] Just as in other areas of medical practice where advances in treatment have created a new population of long-term survivors (eg, patients with head injury and very-low-birth-weight infants), long-term morbidity of children surviving cancer has become an area of greater relevance to physicians, patients, and educators.

Radiation and many chemotherapeutic agents have potentially toxic side effects that may be immediate or delayed, transient or permanent.[4,5] When these therapies are directed to the CNS, either as intrathecal chemotherapy (IT-Chemo) or cranial radiotherapy (CRT), there is a potential for serious cognitive sequelae. Although rare, leukoencephalopathy is the most severe sequela of CNS therapy and is characterized by a progressive dementia with neurological impairment, sometimes ending in coma and death. The increased vulnerability of the pediatric patient with cancer to long-term cognitive sequelae related to treatment has been well documented.[6-10] Many studies have shown that chemotherapy alone (even moderate doses of intrathecally administered methotrexate) does not appear to have long-term effects on higher cognitive functions in children with tumors outside the CNS.[6,10-14] Cranial radiotherapy, on the other hand, has often been associated with serious, long-term cognitive sequelae, especially when administered at a young age[6,10,15-17] and concurrently with intrathecal methotrexate.[18] Declines in intellectual abilities, academic achievement, memory, fine motor, and visuomotor abilities are often attributed to the use of CRT. Similar to the deficits seen in patients suffering white-matter damage caused by closed head injury or congenital hydrocephalus,[19,20] the deficits in patients treated with CRT are more common and more pronounced in nonverbal, abstract reasoning, and attentional abilities.[6,10,21] Caution is warranted, however, in attributing all of the deleterious effects of treatment to CRT because of the possible synergistic effect of combination therapies consisting of IT-Chemo or high-dose intravenous methotrexate and CRT.

Neuropsychological sequelae of CRT would occur, presumably, because white-matter damage disrupts the normal pattern of anatomical connectivity between brain areas involved in organized, coordinated cognitive activity. Few studies, however, have addressed the underlying physiological basis of these deficits, even though physiological measures may be more sensitive to detection of subtle disruptions of myelination than anatomical imaging is. Measures of brain electrophysiology and speed of cognitive processing seem to be well suited for study since both should be affected by white-matter damage. Electro-

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Table 1.—Demographic, Disease, and Treatment Characteristics of Study Patients*

Patient No./Sex/Race	Age, y		Years Since Diagnosis	Diagnosis	Treatment				
					Chemotherapy			CRT	
	Diagnosis	Test			Systemic	IT-Chemo	High-Dose Methotrexate	Age, mo	Treatment Regimen
1/F/B	1.0	12.8	11.8	Unclassified sarcoma	+	...	...	...	AVAC
2/M/AH	10.1	17.2	7.1	Ewing's sarcoma	+	...	...	...	AVAC
3/M/AH	2.7	21.0	18.4	Acute lymphocytic leukemia	+	+	...	...	ALL-OUT No. 2, BOMB
4/F/AH	5.9	13.7	7.8	Acute lymphocytic leukemia	+	+	...	...	ALinC No. 13, regimen 1
5/F/W	6.8	15.6	8.8	Acute lymphocytic leukemia	+	+	+	...	ALinC No. 13, regimen 2
6/M/W	10.8	23.4	12.6	Non-Hodgkin's lymphoma	+	+	...	...	SLA2, L-2
7/F/W	2.6	10.7	8.1	Acute lymphocytic leukemia	+	+	+	...	ALinC No. 13, regimen 2
8/F/W	12.2	18.8	6.6	Hodgkin's disease	+	...	...	...	ABVD
9/M/W	1.2	16.1	15.0	Testicular carcinoma	...	...	...	...	Surgery only
10/M/W	3.3	11.5	8.1	Acute lymphocytic leukemia	+	+	...	...	ALinC No. 13, regimen 1
11/M/W	11.8	18.9	7.2	Burkitt's lymphoma	+	+	+	...	Pediatric Oncology Group protocol No. 81-06
12/M/W	0.3	22.4	22.1	Wilms' tumor	+	...	...	...	Actinomycin D=vincristine
13/M/W	1.3	16.2	14.9	Acute myelomonocytic leukemia	+	+	...	...	mini-COAP, CNS No. 5
14/M/W	4.3	23.6	19.4	Acute lymphocytic leukemia	+	+	...	...	ALinC No. 9
15/F/W	4.8	13.3	8.5	Acute lymphocytic leukemia	+	+	...	...	ALinC No. 113, regimen 1
16/M/AH	4.3	11.1	6.8	Burkitt's lymphoma	+	+	+	...	Pediatric Oncology Group protocol No. 81-06
17/F/AH	1.4	11.9	10.5	Acute lymphocytic leukemia	+	+	...	...	ALinC No. 12, regimen 3
18/M/W	6.1	16.5	10.4	Ewing's sarcoma	+	...	...	...	AVAC
19/F/AH	0.9	11.1	10.2	Wilms' tumor	+	...	...	...	National Wilms Tumor No. 3, Reg. L/K
20/M/AH	2.7	23.4	20.7	Rhabdomyosarcoma	+	...	...	...	VAC (modified)
21/M/AH	0.3	16.3	16.1	Neuroblastoma	+	...	...	...	AVAC+DTIC
22/M/W	2.2	21.1	18.9	Acute lymphocytic leukemia	+	+	...	...	ALL-OUT No. 2, Djerassi methotrexate, BOMB
23/M/W	15.9	25.4	9.5	Acute myelomonocytic leukemia	+	+	...	16.2	Pediatric Oncology Group protocol No. 18-01
24/M/W	2.5	16.0	13.5	Acute lymphocytic leukemia	+	+	...	2.5	ALinC No. 12, Reg. 1, ACOP+CNS No. 5
25/F/AH	13.5	30.7	17.2	Acute lymphocytic leukemia	+	+	...	13.6	ALinC No. 10, ALINC No. 11, SIMAL No. 1
26/F/W	2.2	15.9	13.7	Acute lymphocytic leukemia	+	+	...	2.3	ALinC No. 12, regimen 1
27/F/W	4.2	21.7	17.5	Acute lymphocytic leukemia	+	+	...	4.3	CALASP-GG, ALINC No. 11, D
28/F/W	8.6	21.8	13.2	Acute granulocytic leukemia	+	+	...	8.8	AGL No. 1 pilot
29/F/W	3.3	15.2	11.9	Acute lymphocytic leukemia	+	+	...	3.4	ALinC No. 12, regimen 1

Table 1.—Demographic, Disease, and Treatment Characteristics of Study Patients* (cont)

					Treatment				
					Chemotherapy			CRT	
Patient No./Sex/Race	Age, y Diagnosis	Test	Years Since Diagnosis	Diagnosis	Systemic	IT-Chemo	High-Dose Methotrexate	Age, mo	Treatment Regimen
30/M/W	2.5	17.7	15.2	Acute lymphocytic leukemia	+	+	. . .	2.6	ALinC No. 11, regimen D
31/M/B	1.8	20.8	19.0	Acute lymphocytic leukemia	+	+	. . .	3.2	ALL-OUT No. 2, CNS No. 5, PIP
32/M/AH	14.8	21.7	7.0	T-cell leukemia	+	+	. . .	14.8	T-3-A, with LSA-2, L-2
33/F/W	1.4	20.0	18.6	Acute lymphocytic leukemia	+	+	. . .	1.5	St Jude's protocol No. 5

*CRT indicates cranial radiotherapy; IT-Chemo, intrathecal chemotherapy; AVAC, dactinomycin (actinomycin D), vincristine, adriamycin, and cyclophosphamide; AH, American Hispanic; ALL-OUT, acute lymphocytic leukemia-out; BOMB, vincristine, daunomycin, prednisone, and cytoxan; ALinC, acute leukemia in childhood; LSA2, lymphosarcoma, protocol 2; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; mini-COAP, mini–cytoxan, Oncovin (vincristine sulfate), cytosine arabinoside, and prednisone; CNS, central nervous system; Reg.L/K, regimen L/K (where L and K are particular regimens used); VAC, vincristine, adriamycin, and cyclophosphamide; DTIC, dimethyl-triazeno-imidazole-carboxamide (dacarbazine); ACOP, adriamycin, cytoxan, Oncovin (vincristine), and prednisone; SIMAL, adriamycin, prednisone, thioguanine, and vincristine; CALASP-GG, vincristine, prednisone, L-asparaginase, and regimen GG; AGL, acute granulocytic leukemia; PIP, purinethol and prednisone; T-3-A, adriamycin for T-cell leukemia; LSA, lymphosarcoma; and L-2, leukemia, protocol 2.

encephalographic (EEG) and evoked potential (EP) procedures have been used in a variety of patient populations to demonstrate pathological changes in demyelinating diseases, even in presymptomatic patients.[22-24] These techniques have also been successful in detecting the neuropathological conditions underlying cognitive dysfunction in patients suffering strokes, various types of dementia, or head injury; in children with specific types of learning disability[25-28]; and in patients with demyelinating diseases such as multiple sclerosis in which EPs have a diagnostic role because of their sensitivity to demyelination. As yet, electrophysiological measures of brain function have not been systematically applied to a population of patients with cancer to help explain cognitive sequelae related to treatment. In this study, we describe the relationship between the P300 event-related potential (ERP), measures of reaction time (RT), and cognitive functioning in a group of long-term survivors of childhood cancer.

Table 2.—Test Instruments and Composition of Neuropsychological Domains

Intelligence	Wechsler Intelligence Scale for Children–Revised (WISC-R)[29] Wechsler Adult Intelligence Scale[30] Stanford-Binet, 4th ed[31]
Academic achievement	Wide Range Achievement Test–Revised[32] Peabody Individual Achievement Test[33]
Language	Information, Similarities, and Comprehension subtests from WISC-R[29] Verbal Fluency–The F-A-S Test[34]
Memory	Verbal Selective Reminding Task[35] Nonverbal Selective Reminding Task[36]
Visuospatial	Beery Visual-Motor Integration Test[37] Block Design subtest from WISC-R[29]
Motor	Finger Tapping: dominant and nondominant hands[38] Grooved Pegboard[38]
Attention	Trailmaking Test, parts A and B[38] Freedom from Distractibility Deviation Quotient (FDDQ)
FDDQ	Arithmetic, Digit Span, and Coding subtests of WISC-R[29]

SUBJECTS AND METHODS

All subjects who met the criteria for the study and who were available for assessment were invited to participate. No subject had been referred for clinical purposes. Criteria for study participation included having been treated for cancer before the age of 16 years, being without any therapy and in complete and continuous remission for at least 5 years, speaking English, and having no past or present neurological or psychiatric illness unrelated to the original diagnosis. Thirty-three patients met these criteria and agreed to participate in the study. Seven additional patients who had been treated for a brain tumor also participated, but their data are not included in this report.

Study procedures were explained to all subjects, and each gave informed consent according to institutional guidelines. Demographic, medical, and treatment data for the group are presented in Table 1. Age at the time of diagnosis ranged from 3 months to almost 16 years (mean [±SD], 5.1±4.7 years). Age at the time of participation in this study ranged from 10.7 years to 30.7 years (mean, 18.0±4.7 years). Type of cancer varied, but most patients had some form of leukemia. Treatment consisted of different combinations of systemic chemotherapy, IT-Chemo, and/or CRT. Four patients had also been treated with high-dose intravenous methotrexate in addition to other systemic and IT-Chemo agents, and one patient had received no therapy other than surgical tumor excision.

To investigate the relationships among treatment, long-term neuropsychological outcome, and brain function, patients were grouped according to whether they had been treated with systemic chemotherapy plus IT-Chemo (IT-Chemo group; n=13) or with systemic chemotherapy, IT-Chemo, and CRT (IT-Chemo+CRT group; n=11). Within the IT-Chemo group, there were eight male and five female subjects. Nine were white and four were American Hispanics. Within the CRT group, there were five male and six female subjects. Eight were white, one was black, and two were American Hispanic. Four patients in the IT-Chemo group also received high-dose methotrexate, which is thought to act as a CNS agent because it crosses the blood-brain barrier. A

Table 3.—Demographic Data and Neuropsychological Status for Three Treatment Groups*

Age and Test Data	No CNS Therapy (n=9)	Systemic+IT-Chemo (n=13)	IT-Chemo+CRT (n=11)	1-Way ANOVA, *P*	Significant Post Hoc Tests		
					A	B	C
Diagnosis age, y	4.0±4.5	4.7±3.3	6.5±5.7	NS	...	...	...
Test age, y	15.1.±4.8	14.0±3.6	17.7±5.5	NS	...	...	...
CRT age, y	...	...	6.7±5.6	...	...	...	...
Intelligence							
Verbal IQ	102.2±14.9	97.0±11.7	93.0±15.7	NS	...	...	...
Performance IQ	110.4±14.2	107.9±14.5	91.9±12.3	<.01	...	+	+
Full-Scale IQ	106.0±11.4	101.9±10.6	91.7±14.1	<.04	...	...	+
Neuropsychological domains							
Academic achievement	100.2±13.6	99.1±5.9	84.6±15.2†	.01	...	+	+
Language	11.1±2.3	9.8±2.0	9.5±3.1	NS	...	...	...
Memory	9.1±2.6	11.1±3.8	7.5±3.7‡	NS	...	+	+
Visuospatial	10.2±2.2	9.8±2.3	7.0±3.0†	<.02	...	+	+
Somatosensory	14.2±3.0	12.4±4.5	8.9±2.4	<.05	...	...	+
Fine motor	12.7±4.0	11.6±4.8	9.3±3.7	NS	...	...	...
Attention	8.5±4.5	9.5±3.4	4.9±2.1§	<.01	...	+	+
Distractibility	10.3±2.0	10.1±2.2	7.8±2.1†	<.02	...	+	+

*Values are mean±SD. Scores were standardized from a normative sample with a mean (±SD) of 100±15 for intellectual and academic domains and a mean of 10±3 for all other domains. CNS indicates central nervous system; IT-Chemo, intrathecal chemotherapy; CRT, cranial radiotherapy; and ANOVA, analysis of variance. Under post hoc comparisons, plus indicates comparisons significant at $P<.05$: A, no CNS treatment vs systemic and IT-Chemo; B, IT-Chemo vs IT-Chemo+CRT; and C, no CRT (combination of no CNS treatment and IT-Chemo groups) vs CRT.

†Group mean significantly below normative means, $P<.01$.

‡Group mean significantly below normative means, $P<.05$.

§Group mean significantly below normative means, $P<.001$.

control group consisted of patients who were treated only with systemic chemotherapy or surgery (No-CNS-treatment group; n=9). Six of the control patients were male and three were female. Four were white, one was black, and four were American Hispanic. A group of normal, healthy comparison subjects was not used because it was believed they would provide inadequate control for the psychological effects of cancer and cancer treatment.

The procedures used consisted of (1) a comprehensive neuropsychological battery, (2) measures of RT, and (3) P300 ERPs. Reaction time and ERP procedures were used because of their sensitivity to cortical white-matter damage and because pathological changes in white matter have been seen in patients following treatments involving CNS chemotherapy and irradiation.

Neuropsychological Testing

All patients were examined with a battery of neuropsychological tests either before or concurrently with this study. Intellectual functioning was assessed using either the Wechsler Intelligence Scale for Children—Revised[29] or the Wechsler Adult Intelligence Scale.[30] In addition to these intellectual measures, patients were also administered neuropsychological tests that assess a wide range of abilities and are standardized with age-based norms. To reduce the variable-to-subject ratio, individual tests were grouped into domains representing more general functions: intellectual, academic achievement, language, memory, visuospatial, somatosensory, motor, attention, and distractibility (Table 2).[29-38]

Reaction Time

Two different conditions were presented by computer program to assess motor reaction speed. Trials (warning tone–response light pairs) were separated by intervals varying randomly from 10 to 20 seconds, and RTs accurate to within 1 millisecond were recorded and averaged for 30 trials in each condition. One condition used a fixed interval of 4 seconds between the warning tone and the visual response stimulus, whereas in the other condition the interstimulus interval (ISI) varied randomly from 1 to 6 seconds. Because six different ISIs were in the random condition, five trials at each ISI were recorded (for a total of 30). The fixed ISI condition gives an indication of response planning and temporal estimation and is prolonged in patients with frontal lobe dysfunction. The random ISI condition gives an indication of concentration and distractibility because the subject must maintain a high state of readiness for 1 to 6 seconds. It was hypothesized that patients whose treatment included CRT would, because of its association with white-matter changes, have diminished CNS processing speed (ie, longer RTs) than would patients treated without CRT.

P300 Event-Related Potential

Cortical auditory evoked responses were recorded according to a P300 paradigm. The P300 response is considered to be an endogenous brain potential that reflects cognitive activity and has been used to infer cognitive dysfunction in a variety of patients with neurological and psychiatric disorders, as well as in patients with cognitive impairment secondary to cerebral trauma or disease.[39] In our study, the patient was presented with a series of 200 tones with a 1-second ISI generated by a computer program. A frequent tone (2000 Hz, 40 milliseconds) occurred on 80% of the trials, and a rare tone (1500 Hz, 40 milliseconds) was interspersed unpredictably in 20% of the trials. The program was designed so that the rare tone never occurred twice in a row. During one series, the computer triggered the signal averaging system simultaneously with the presentation of the frequent tones, and the patient was instructed simply to relax and listen. We recorded only every fifth frequent tone so that this series would more closely match the rare tone series in total duration and number of sweeps averaged. During the other series, the computer triggered the signal averaging system simultaneously with the presentation of the rare tone, and the patient was instructed to count the number of rare tones. A total of 35 to 40 sweeps was averaged for each tone condition, resulting in waveforms with clearly distinguishable peaks. Electrodes were placed at the vertex (C_z) referenced to linked earlobes and with a forehead ground. Impedances were maintained below 5 kΩ. Electroencephalographic activity was amplified by 200 000, bandpass filtered from 0.3 to 30 Hz with a

60-Hz notch filter (Model 12 A-5, Grass Instrument Co, Quincy, Mass), and averaged online over a duration of 600 milliseconds after stimulus with a resolution of 1 millisecond (Model ISC-16 E/CR, R. C. Electronics, Goleta, Calif). Separate averages were obtained for the rare and frequent tone conditions. Patients were observed during the evoked response procedure to detect and rectify overt behaviors that might reduce the quality of the recording. This was seldom necessary, however. Recordings with excessive muscle artifact or interference were discarded and repeated. Latency and amplitude of the major components of the ERP (P1, N1, P2, and P3) were measured with electronic cursors, and it was hypothesized that patients treated with CNS therapy, especially CRT, would show longer latency and smaller amplitude of the P300 component of the ERP.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to investigate group differences in neuropsychological performance, RT, and ERP measures. To investigate further the effects of specific therapy regimens, we then conducted planned post hoc analyses (*t* tests with Bonferroni correction for multiple comparisons) comparing neuropsychological, RT, and ERP results of the different groups to address the following questions: (1) Are patients who received IT-Chemo significantly different from those who received only systemic chemotherapy? (2) Are patients who received CRT (in addition to IT-Chemo) significantly different from those who received only IT-Chemo? (3) Are patients who received CRT significantly different from those who did not receive CRT (the No-CNS-treatment group combined with IT-Chemo group)?

Correlational techniques were then used to examine the relationship between the experimental measures (RT and ERP) and neuropsychological performance. Pearson correlations were calculated to determine which of the experimental measures were significantly correlated with performance on the various neuropsychological domains.

RESULTS

At diagnosis, patients ranged in age from 3 months to 16 years (5.1±4.7 years). When examined, patients ranged from 10.7 to 30.7 years old (18.0±4.7 years), and the elapsed time since diagnosis ranged from 6.6 to 22.1 years (12.9±4.7 years). Groups were comparable with respect to age at diagnosis, race, and gender (Tables 1 and 3).

Neuropsychological Test Results

Intelligence scores were within the normal range for all three groups but followed a gradient of performance in which those patients who received the least intensive therapy (systemic chemotherapy) had the highest scores, followed first by those who had treatment that included IT-Chemo, and then by those whose treatment included CRT in addition to IT-Chemo (Table 3). This pattern was statistically significant for Performance and Full-Scale IQs but not for Verbal IQ. Statistically significant group differences were also obtained for the academic achievement, visuospatial, somatosensory, and attention domains. Scores on most of these domains showed the same association with treatment group as seen in the intellectual scores. However, attention and memory domain scores were slightly (insignificantly) lower in the No-CNS-treatment group than in the IT-Chemo group. Mean scores for these domains were still lowest in the CRT group.

Because statistically significant group differences do not necessarily indicate significant real-world impairment (eg, one group may be average and the others well above average), we also compared group mean scores with the age-standardized normative mean scores. Mean scores for the IT-Chemo group were all within the normal range in contrast to mean scores of patients in the IT-Chemo+CRT group, which were significantly impaired in five of eight cognitive domains (academic achievement, memory, visuospatial, attention, and distractibility). The latter group's lowest mean score was in the attention domain, which was almost 2 SDs below age-standardized norms. Group means for the No-CNS-treatment group were within the normal range for all cognitive domains.

Post Hoc Group Comparisons of Neuropsychological Test Results

No-CNS-Treatment vs IT-Chemo Groups.—Although the No-CNS-treatment group scored slightly higher than the IT-Chemo group in most areas tested, it scored slightly lower in memory and attention. However, these differences were not statistically significant, nor were there significant differences between these two groups on the intellectual scales or on any of the other cognitive domains.

IT-Chemo vs IT-Chemo+CRT Groups.—Patients who had received combination therapy consisting of IT-Chemo and CRT had lower performance scores in all intellectual and cognitive domains. Performance IQ, but not Verbal IQ, was significantly lower (by >1 SD) than in the other groups. Statistically significant differences were found also in the academic achievement, memory, visuospatial, attention, and distractibility domains.

No-CRT vs CRT Groups.—When the patients were grouped according to whether CRT had been included as part of their treatment regimen, it was clear that inclusion of CRT in the treatment regimen had a negative impact on their neuropsychological outcome. Mean Performance and Full-Scale IQ scores were significantly lower for the CRT group than for the No-CRT group, although all were within the average range (±1 SD). There was almost a 1-SD difference between the groups in Performance IQ, but much of this difference was accounted for by the slightly higher than average mean score of the No-CRT group. Mean scores for Verbal IQ were not significantly different.

Scores for the CRT group were significantly lower in six of the eight cognitive domains: academic achievement, memory, visuospatial, somatosensory, attention, and distractibility. Many of the domain scores of the CRT group were significantly below normative means (discussed above) and suggest that multiple areas of cognitive deficit, especially attention and memory, may contribute to deficits in academic achievement.

The CRT group was older at the time of testing (by almost 4 years) than the No-CRT group, but the age difference is unlikely to have had an effect on the results, because the norms used for the various cognitive tests were standardized by age; the individual test items for different ages vary by difficulty but not by content. There was, however, a significant correlation between age at the time of evaluation and academic achievement (r=.39, P<.04). There were no significant correlations between age at diagnosis or age at the time of evaluation with any other domain score.

In summary, children treated for cancer are at risk for intellectual and cognitive impairment. The use of IT-Chemo+CRT seems to carry the highest risk of sequelae, whereas treatment consisting of systemic chemotherapy and IT-Chemo without CRT has minimal effects on neuropsychological status.

Table 4.—Reaction Time (Milliseconds) of Three Treatment Groups

	No CNS Therapy (n=9)	Systemic and IT-Chemo (n=8)	CRT (n=10)	1-Way ANOVA
Random ISI	293.3±41.3	336.8±56.8	397.4±66.0	$P<.002$
Fixed ISI	270.3±38.9	276.7±39.0	386.0±48.1	$P=.0001$

*Values are mean±SD. CNS indicates central nervous system; IT-Chemo, intrathecal chemotherapy; CRT, cranial radiotherapy; and ANOVA, analysis of variance. By post hoc tests, for both random and fixed ISI conditions, $P<.05$, no CRT (combination of no CNS treatment and IT-Chemo groups) vs CRT, and IT-Chemo vs IT-Chemo+CRT.

Reaction Time

There was a gradient of reaction speed for the three patient groups on each of the RT tasks. Patients who received no CNS therapy had the fastest RTs, followed by those who had treatment that included IT-Chemo but not CRT. Patients whose treatment included CRT had the slowest RTs. Group differences were statistically significant in both the random and the fixed ISI procedures (Table 4 and Fig 1). There was also a significant effect for the RT condition when all groups were combined. Reaction times for the random condition were consistently slower than the fixed condition (F=4.34, *df*=1,22, $P<.05$).

Post Hoc Group Comparisons of RT

No-CNS-Treatment vs Systemic Chemotherapy and IT-Chemo Groups.—Mean RT of the IT-Chemo group was approximately 15% slower than that of the No-CNS-treatment group during the random ISI condition and approximately 2% slower during the fixed ISI condition. However, these differences were not statistically significant.

IT-Chemo vs IT-Chemo+CRT Groups.—Mean RT of the IT-Chemo+CRT group was approximately 18% slower than that of the group given only IT-Chemo during the random ISI condition and approximately 40% slower during the fixed ISI condition. These differences were statistically significant ($P<.05$).

No-CRT vs CRT Groups.—Mean RT for both the random and fixed ISI conditions was significantly slower for patients treated with CRT than for those treated only with systemic and/or IT-Chemo (Table 4).

During the fixed ISI condition, subjects learn to estimate the interval (4 seconds) and can anticipate the occurrence of the response stimulus, thereby improving their speed. This is not possible, however, during the random ISI condition, in which the ISI varies unpredictably from 1 to 6 seconds. Ordinarily, subjects show an improved RT during the fixed ISI condition compared with the random ISI condition because of their ability to make temporal estimations. Therefore, we compared the RTs of patients who were or were not treated with CRT during these two conditions in a mixed-design ANOVA with repeated measures. Because there is also an effect of ISI on RT during the random ISI condition (longer ISI results in shorter RT; Fig 1, left), we compared the RT during the 4-second random ISI with the fixed ISI RT (also 4 seconds). The mean RT for the No-CRT group became faster (improved) from 313.7±69.3 milliseconds during the random ISI condition to 272.6±38.9 milliseconds during the fixed ISI condition, but the mean RT for the CRT group became slower: 378.3±58.3 milliseconds during the random vs 386.0±48.1 milliseconds during the fixed ISI conditions. This interaction was statistically significant (F=4.32, *df*=1,23, $P<.05$), indicating that patients in the CRT group failed to take advantage of the added information (length of time between warning and response stimuli) available during the fixed ISI condition.

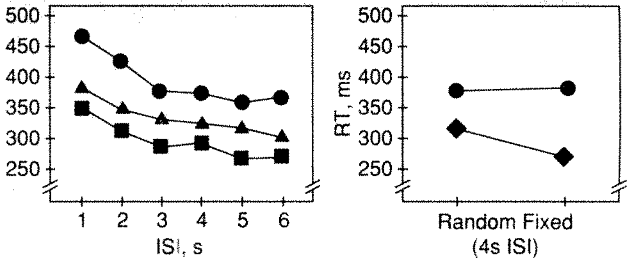

Fig 1.—*Reaction time (RT) data for three treatment groups. Left, Random interstimulus interval (ISI) (1 to 6 seconds). Right, Comparison of random and fixed ISIs (each 4 seconds) for those treated with cranial radiotherapy (CRT, circles) vs those treated without CRT (two groups combined, diamonds). In the left graft, triangles indicate intrathecal chemotherapy; squares, no central nervous system treatment.*

Table 5.—Correlations of Reaction Time and Event-Related Potential Measures With Neuropsychological Performance for All Patients Combined*

	Reaction Time		P300	
	Fixed ISI	Random ISI	Latency	Amplitude
Verbal IQ	−.20	−.39†	−.15	.26
Performance IQ	−.71‡	−.56‡	−.45†	.34
Full-Scale IQ	−.59§	−.58‡	−.37	.38
Academic achievement	−.33	−.45†	−.26	.41†
Language	−.27	−.34	−.10	.14
Memory	−.31	−.21	−.07	.27
Visuospatial	−.54§	−.62‡	−.53§	.30
Somatosensory	−.58§	−.30	−.29	.33
Motor	−.52§	−.51§	−.36	.15
Attention	−.45†	−.36†	−.16	.46†
Distractibility	−.53†	−.49§	−.25	.50§

*ISI indicates interstimulus interval.
†$P<.05$.
‡$P<.001$.
§$P<.01$.

Significant ($P<.05$) negative correlations were obtained between RT and neuropsychological performance in all cognitive domains except memory, indicating that faster RT was associated with higher test scores (Table 5). There were no significant correlations between RT and age at diagnosis or age at the time of assessment.

P300 Event-Related Potential

Significant group differences in the latency and amplitude of the P300 ERP were obtained. As in the RT measures and in the scores on some of the intellectual and cognitive domains, there was a statistically significant gradient of P300 latency, whereby patients treated without any therapy to the CNS had the shortest latency, followed by those treated with IT-Chemo, and finally those treated with CRT (Table 6). There was also a significant difference between the groups in P300 amplitude, but mean amplitudes did not

Table 6.—Latency and Amplitude of the Major Cortical Evoked Potential Components During P300 Procedure*

	No CNS Therapy (n=9)	Systemic and IT-Chemo (n=8)	IT-Chemo +CRT (n=10)	1-Way ANOVA, *P*
P1				
Latency	59.3±38.6	45.6±18.4	47.7±19.3	NS
Amplitude	−0.1±1.6	−0.3±1.7	−0.1±2.6	NS
N1				
Latency	112.4±26.4	108.7±19.0	116.7±12.5	NS
Amplitude	−5.0±1.8	−7.6±2.0	−6.3±3.3	NS
P2				
Latency	179.7±28.7	182.3±23.0	186.4±22.8	NS
Amplitude	1.6±2.8	2.8±3.1	4.4±2.9	NS
N1 to P2				
Amplitude	6.6±2.0	10.4±3.0	10.7±5.3	.055
P300				
Latency†	327.3±52.5	346.3±11.1	373.7±20.8	.02
Amplitude†‡	7.1±1.8	9.6±2.3	5.6±2.2	<.003

*Values are mean±SD, with latency measured in milliseconds and amplitude, microvolts. CNS indicates central nervous system; IT-Chemo, intrathecal chemotherapy; CRT, cranial radiotherapy; ANOVA, analysis of variance; and NS, not significant.

†*P*<.05, no CRT (combination of no CNS treatment and IT-Chemo groups) vs CRT.

‡*P*<.05, IT-Chemo vs IT-Chemo+CRT.

follow the same pattern discussed above. Patients in the IT-Chemo group had the highest P300 amplitudes and those in the CRT group had the lowest, whereas patients in the No-CNS-treatment group had intermediate amplitudes.

We also examined earlier peaks of the cortical EP obtained during the P300 recording (Fig 2) and the brain-stem EP to determine whether group differences that suggest sensory or attentional, rather than cognitive, factors account for the results. There were no statistically significant group differences in latency or amplitude of the brain-stem EP or the earlier cortical components, indicating that differences observed in the P300 were due to differences in the cognitive registration of the novel stimulus rather than to other factors.

Post Hoc Group Comparisons of P300 Latency and Amplitude

No-CNS-Treatment vs IT-Chemo Groups.—Mean group values for latency and amplitude of the P300 were not significantly different for these two groups.

IT-Chemo vs IT-Chemo+CRT Groups.—Mean P300 latency values were not significantly different, but mean P300 amplitude was significantly smaller in the IT-Chemo+CRT group than in the IT-Chemo group.

No-CRT vs CRT Groups.—Mean P300 latency was significantly shorter and amplitude significantly larger for the No-CRT group than for the CRT group.

The RT was significantly correlated with P300 latency (r=.55, df=26, $P<.004$) and with P300 amplitude (r=−.39, df=26, $P<.05$), indicating that faster RT is associated with a quicker and larger P300. Neuropsychological performance in all domains correlated negatively with P300 latency and positively with P300 amplitude, indicating faster and greater cognitive registration of the rare stimulus among patients with higher scores (Table 5). These results suggest that cognitive registration of a rare and unpredictable sensory event is slower and less meaningful in patients whose treatment included CRT. There were no significant correlations between P300 latency or amplitude and age at diagnosis or age at the time of assessment.

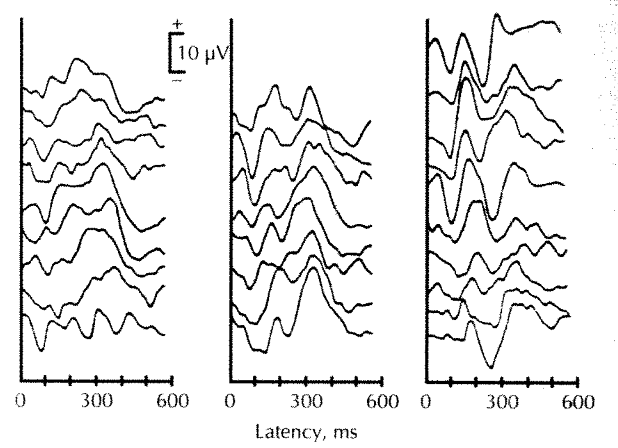

Fig 2.—*Group composites of cortical event-related potential waveforms recorded to the rare tone during the P300 procedure. Left, Group receiving no central nervous system therapy; center, group receiving systemic and intrathecal chemotherapy; and right, group receiving intrathecal chemotherapy and cranial radiotherapy.*

COMMENT

This study examined neuropsychological test performance, motor reaction speed, and P300 ERPs in a group of 33 long-term survivors of childhood cancer in an attempt to describe the underlying physiological basis of treatment-related cognitive sequelae. We tested the hypothesis that treatment regimens that included intense CNS treatment, particularly CRT, would be associated with cognitive sequelae and with slowing of cortical processing.

On the intelligence scales and most of the cognitive domains, scores followed a gradient, with the No-CNS-treatment group scoring highest, followed by the IT-Chemo group, and then the CRT group. Although the IT-Chemo group's scores were consistently lower than those of the No-CNS-treatment group (nine of 11 intellectual and cognitive measures), their scores were all within the normal range, and the differences were small and not statistically significant. Significant differences in cognitive function were found, however, when the scores of these groups were compared with the scores of the CRT group. Patients treated with CRT had preserved language function but had deficits in memory, visuospatial, and attentional abilities, which probably contributed to their somewhat lower than average intellectual scores and their deficit in academic achievement. The RT measures showed an even stronger and more consistent trend among the treatment groups, whereby diminished speed was associated with more intensive therapies. Differences among the three groups on mean RT were as high as 35% during the random condition and 43% during the fixed condition. Patients in the CRT group also failed to benefit from the advantage of the fixed ISI condition and actually had longer RTs relative to those obtained during the more ambiguous random ISI condition, a pattern that was opposite to that of the nonirradiated patients. This finding suggests that patients whose treatment includes CRT have difficulty focusing attention, a skill necessary for efficient response planning. This idea is supported by the finding that attention domain scores were their weakest area on the neuropsychological tests, with scores falling well below the normative mean. Differences in the latency of the P300 peak were not as large as the RT results but reflected the same trend, which suggests that both measures are useful metrics of cognitive processing speed that are sensitive to treatment effects. Correlations between these measures and neuropsychological test scores further reinforce their utility in helping explain the physiological basis of treatment-related cognitive sequelae.

Because the therapeutic effects of chemotherapy and radiotherapy are accomplished through their disruption of frequently dividing cells, and because the CNS is thought to be in a state of continued growth, development, and myelination throughout early childhood,[40-46] it has been postulated that children would be at greater risk for treatment-related cognitive sequelae than are older patients. Pathological effects of CRT on the brain have been well documented. Mineralizing microangiopathy, cerebral calcifications, and white-matter necrosis may eventually develop[5,47-49] and are often visible on neuroimaging scans. The etiology of these neuropathic changes is poorly understood, but several direct and indirect mechanisms have been proposed.[50] Damage to the genetic material of cerebrovascular endothelial cells may affect the CNS indirectly as a delayed effect of CRT, or glial cells may suffer more direct genetic damage from CRT, resulting in decreased cell proliferation. Glial cells are probably more vulnerable in young patients, whereas cerebrovascular endothelial cells are sensitive in persons of all ages.[51] Although some studies have suggested a relationship between these anatomical changes and neuropsychological deficits,[52,53] a definite link has not always been demonstrated, perhaps because of the difficulty in objectively quantifying and characterizing white-matter changes in vivo. Because myelination increases axonal conduction velocity, disruption of myelin impedes nerve transmission speed and may result in slowing of cognitive processes and disruption of the normal patterns of cortical connectivity required for integrated, coordinated, higher cognitive processes.

Studies using EEG and EP recordings in patients with cancer have been infrequent, usually being performed only as an adjunct to a medical study or for clinical purposes. Typical findings have included slowing of the EEG frequency and alteration of the latency and amplitude of the auditory and visual EPs.[54-57] Martino et al,[54] for instance, reported on two patients with lymphoma in whom transient dysphasia, quadriparesis, and EEG abnormalities developed 10 days after they had completed a regimen of moderate-dose methotrexate. Epstein et al[58] found persistently depressed EEG frequency in 13 children with acute lymphocytic leukemia (ALL) treated with IT-Chemo. Increased latency of the visual EP has been associated with chronic progressive myelopathy in patients with leukemia.[59] Clinical EEG and short- and long-latency EPs are not necessarily sensitive to cognitive function, however, except in patients with severe impairment.

Only one other study has used a measure of endogenous brain activity to describe treatment-related cognitive sequelae in patients with cancer in a planned study design. Heukrodt and associates[60] recorded the P300 ERP in three groups of long-term survivors: patients with solid tumor with no CNS treatment and two groups of patients with leukemia who were treated with CNS prophylaxis. They found prolonged P300 latency and evidence of cognitive impairment in all three patient groups. They concluded that even systemically administered chemotherapy in patients with solid tumors outside the CNS may place them at risk for the types of neuropsychological deficits commonly attributed to CNS treatment. These results are surprising because there appears to be no explanation for cortical effects of systemic chemotherapy (other than high-dose intravenous methotrexate, which, because of its extremely high concentration, crosses the blood-brain barrier), and few studies have reported cognitive effects other than transient peripheral motor and somatosensory changes from systemic chemotherapy.[10-12] There were no significant differences in P300 latency between their group of patients with solid tumors and their groups of patients receiving CNS treatment. As in the current study, their findings of significant negative correlations between P300 latency and cognitive measures indicated that longer P300 latencies were associated with lower neuropsychological performance. Significant effects of IT-Chemo dose and cognitive performance were also reported. Unfortunately, no comparisons were made between patients treated with or without CRT, so it is impossible to determine whether it was chemotherapy or CRT, or their combination, that was responsible for these effects.

Our results are consistent with those of Heukrodt et al[60] except that we found preserved cognitive function in patients treated without CRT, even if they were treated with CNS chemotherapy. This finding is consistent with a previous report[61] and suggests that there is not a synergistic effect between IT-Chemo and CRT on neuropsychological test performance. Our findings of intermediate values in RT and P300 latency in the presence of preserved neuropsychological test scores in these patients suggests that IT-Chemo may have subtle yet long-lasting effects on the brain that are not strongly manifested as cognitive impairment.

These results indicate that when treatment consists of CRT with IT-Chemo, there are long-term effects of treatment on brain and cognitive function that are not present, or are present to a much lesser degree, when treatment excludes CRT. Of course, without a group of patients treated with CRT only, one must be cautious in attributing all of the effects to CRT. Of perhaps greater interest than the neuropsychological results, which are consistent with previous reports that have been extensively reviewed,[6] is the finding that simple measures of speed and organization of cortical processing are related to cognitive functioning and treatment regimen in long-term survivors of cancer. This supports the idea that intensive CNS therapy, especially CRT, induces white-matter changes that slow down mental activities to such a degree that cognition is impaired. It follows that children who have such cognitive impairments may benefit from educational situations in which time constraints are not placed on problem-solving tasks. Alternatively, cognitive remediation to increase speed of cognitive processing may help alleviate some of these problems and allow children to attain higher levels of academic achievement as a result.

Electrophysiological and neurobehavioral measures of brain activity appear to have great utility for demonstrating the physiological correlates of cognitive function related to treatment for childhood cancer. Further studies, perhaps in a longitudinal design, using cognitive EPs and spectral analysis of the EEG at rest and during mental activity may help determine the acute and chronic effects of specific therapy regimens on neuropsychological abilities.

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Cerebral White Matter and Cognition in Hydrocephalic Children

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• Although children with hydrocephalus frequently show poor development of nonverbal cognitive skills relative to verbal skills, little is known about the neuropathologic correlates of these discrepancies. In this study, cerebral white-matter structures and lateral ventricles were measured from the magnetic resonance images of age-matched children with meningomyelocele, meningocele, and aqueductal stenosis and normal subjects. The volume of each lateral ventricle and the cross-sectional area of the corpus callosum and internal capsules were correlated with concurrent measures of verbal and nonverbal cognitive skills. The corpus callosum in the meningomyelocele and aqueductal stenosis groups was smaller. The lateral ventricles were larger, and the internal capsules were smaller, in all patient groups than in normal subjects. There were no differences in the size of the centra semiovale. Although verbal and nonverbal measures correlated positively with the size of the corpus callosum, the correlation was higher for nonverbal measures. Nonverbal measures correlated with the right, but not the left, lateral ventricle and with the area of the right and left internal capsules. Verbal measures correlated with the left, but not right, lateral ventricle and with the left, but not right, internal capsule. These results show a relationship between the corpus callosum and cognitive skills that is also influenced by hydrocephalus-related changes in the lateral ventricles and other cerebral white-matter tracts.

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Hydrocephalus associated with aqueductal stenosis (AS) and spinal dysraphism is a common disorder of childhood. Hydrocephalic children frequently lag in their development of cognitive skills. Little is understood about the neuropathologic correlates of these developmental problems, particularly the tendency for these children to show poorer development of nonverbal cognitive skills than language development.[1,2] The underlying cause of the hydrocephalus and/or the complications associated with its treatment are frequently implicated.[1-4] These congenital causes of hydrocephalus are also associated with abnormalities of neuroembryogenesis.[5] Children with neural tube defects commonly have neuropathologic lesions at both ends of the neural tube. Caudally, the usually obvious spina bifida (SB) is associated with a dysraphic spinal cord. The Arnold-Chiari malformation is virtually ubiquitous in children with meningomyelocele (MM), and partial agenesis or hypoplasia of the corpus callosum is common.[5,6] There are other less obvious abnormalities of the brain in children with SB, such as interdigitation of the hemispheres, a small posterior fossa, and other hindbrain anomalies. Children with AS have congenital pathologic changes in the corpus callosum as well as obstructive hydrocephalus; they, unlike children with SB, are generally free of other congenital neuropathologic lesions.[5]

Abnormalities of the corpus callosum are categorized as complete agenesis, partial agenesis, and hypoplasia. The corpus callosum is formed between weeks 8 and 12, and agenesis is generally attributed to an early disruption in neuroembryogenesis.[5,7] Complete agenesis is rare, particularly in SB. More common is partial agenesis of the corpus callosum, which may be present in many cases of AS and SB.[8,9] In addition to a congenital malformation, hydrocephalus per se can stretch and even destroy the corpus callosum, often leading to hypoplasia in which all corpus callosum structures are present but thinned. Other white-matter tracts can also be affected by hydrocephalus, particularly projection fibers near the midline, which connect the hemispheres to the diencephalon and more caudal regions. More lateral white-matter tracts that connect cortical regions within each hemisphere are generally less affected by hydrocephalus.

Children with congenital hydrocephalus infrequently present with frank mental retardation, but many studies have shown poorer development of nonverbal cognitive skills than in verbal cognitive skills in these children.[1-4,10,11] Studies addressing the relationship of brain anatomy and cognitive skills in congenital hydrocephalus have primarily focused on two issues: (1) the presence of hydroceph-

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Table 1.—Age, Race, Gender, and Socioeconomic Status (SES) by Group

	Group			
Variable	**Meningomyelocele**	**Meningocele**	**Aqueductal Stenosis**	**Normal**
N	17	6	9	12
Mean (±SD) age, mo	88.63±6.56	88.40±6.28	90.45±10.88	90.66±5.39
Race, No.				
White	12	4	5	9
Black	1	0	3	0
Hispanic	3	2	0	2
Asian	1	0	1	1
Gender, No.				
M	6	2	6	7
F	11	4	3	5
SES, No.				
Low	9	4	1	4
Middle	4	0	4	6
High	4	2	4	2

alus and its treatment and (2) spinal dysraphism.[1,3,4] These studies have primarily addressed *levels* of cognitive skills and, with two exceptions,[2,11] have not addressed *discrepancies* in verbal and nonverbal cognitive skills. In addition, only one study,[2] which used retrospective air ventriculograms, has attempted to relate discrepancies in cognitive functioning to the condition of the hydrocephalic brain. This study showed that discrepancies in verbal and nonverbal cognitive functioning were associated with AS and, to a lesser extent, SB. These discrepancies were also related to greater posterior than anterior thinning of the cerebral white matter. There are no studies, to our knowledge, correlating cognitive skills with quantitative magnetic resonance (MR) imaging studies in hydrocephalic children or any other acquired neurologic disorder of childhood.

In the present study, quantitative analyses of MR images of the lateral ventricles and cerebral white matter were performed for children with SB or AS and age-matched normal children. Verbal and nonverbal cognitive skills were concurrently assessed. Two sets of questions were examined. The first questions addressed the nature of the pathologic changes above the tentorium. We hypothesized that MR imaging measures would reveal larger lateral ventricles and smaller commissural (corpus callosum) and projection (internal capsule) fiber tracts in hydrocephalic children than in controls, with no difference in the size of tracts that are predominantly association fibers (centrum semiovale). The second set of questions addressed relationships of these measures with verbal and nonverbal cognitive skills. We hypothesized that nonverbal cognitive measures would be related both to the size of the corpus callosum and to internal capsules in the left and right hemispheres. These structures are considered essential for interhemispheric and intrahemispheric communication and have been proposed to play an important role in the development and maintenance of nonverbal cognitive skills.[10] Finally, we hypothesized that lower verbal skills would occur in the presence of larger left lateral ventricles and that lower nonverbal skills would be associated with larger right lateral ventricles.

SUBJECTS AND METHODS

Subjects included 23 children with SB, nine with AS, and 12 normal controls comparable in age, socioeconomic status, and race. It is important to recognize that children were selected at ages where the cognitive skills of interest could be reliably measured. This selection criterion tends to eliminate children with more severe hydrocephalic conditions, who often die by 5 years of age.[5] Table 1 summarizes demographic variables with no significant differences in age, gender, race, and socioeconomic status. Although gender differences were not significant, there was a tendency for the SB group to contain more girls, which is consistent with the epidemiology of the disorder.[6] Children with significant antecedent head injury, infection, or other neurologic disease unrelated to shunting, severe psychiatric disorders, and gross sensory disorder were excluded. The study was approved by the University of Texas Health Science Center–Houston Committee for the Protection of Human Subjects. Child assent and parental consent forms were signed for both the psychometric and MR imaging components of the study.

The SB group was further divided into those with MM (N=17) and meningocele (M; N=6). All children with MM had Arnold-Chiari II malformations, and 15 underwent shunting for hydrocephalus. In 11 (65%) of 17, there was partial agenesis of the corpus callosum, which always included the rostrum. There was also agenesis of the splenium in five of 11 cases with partial agenesis. All 17 cases had hypoplasia of the body and, in nonagenesis cases, the splenium. As expected, 35% were nonambulatory, and 41% ambulated with assistance.

The M group had two children with Arnold-Chiari II malformations, one of whom had hypoplasia of the corpus callosum. One additional child had no Chiari malformation but underwent shunting for hydrocephalus and also had partial agenesis of the corpus callosum involving the rostrum and hypoplasia of the body and splenium. One additional patient had hypoplasia of the corpus callosum. Only one child needed assistance walking.

In the AS group, all underwent shunting for hydrocephalus, and one child had a Chiari I malformation; four of nine had partial agenesis; eight of nine had hypoplastic corpora callosa. All were fully ambulatory. Two additional children with AS who were scanned had complete agenesis and were excluded from this study because movement artifact prevented quantification. Both of these children had moderate mental retardation.

Only seven (four in the MM group and three in the AS group) of the 32 patients were taking anticonvulsants for seizures. In four children, seizures were fully controlled; two children had occasional seizures (one to four) yearly, and one child had monthly seizures. All seven children had complex partial seizures, except for one child who had absence seizures. Two children were taking carbamazepine, two were taking phenobarbital, and the other patients were taking ethosuximide, phenytoin, and both phenytoin and acetazolamide.

Table 2.—Neuropsychological Tests Composing the Verbal and Nonverbal Composites

Verbal	Nonverbal
Auditory Analysis Test[14]	Beery Visual-Motor Integration[18]
Rapid Naming[15]	Judgment of Line Orientation[19]
Word Fluency[16]	
Word-Finding Test[17]	
McCarthy Opposite Analogies, Fluency, Vocabulary[12]	

The normal children were siblings or relatives, or were recruited from families with hydrocephalic children who were not within the age range of the study. All were neurologically intact, with normal MR images.

Each subject received the following assessments of verbal and nonverbal cognitive skills: (1) McCarthy Scales of Children's Abilities,[12] (2) Wechsler Intelligence Scale for Children–Revised (WISC-R),[13] and (3) additional neuropsychological tests measuring verbal and nonverbal skills. From these three sources, indexes of verbal and nonverbal functioning were obtained, including McCarthy Verbal and Perceptual-Performance IQ scores, WISC-R Verbal and Performance IQ scores, and standardized composites of verbal and visual-spatial cognitive functioning derived by averaging scores on the neuropsychological tests.[11] The McCarthy Scales and WISC-R were used because these tests have traditionally been used to demonstrate lower nonverbal than verbal performance in hydrocephalic children. However, the composite IQ scores are contaminated by subtests that require skills other than those identified as "verbal" or "nonverbal." The neuropsychological composites,[14-19] which included subtests from the McCarthy Scales that measure semantic language, are purer measures of the constructs of interest and are summarized in Table 2. That all six variables measure the skills of interest, albeit with varying degrees of precision, is well established by psychometric studies[1,10-13] and studies of hydrocephalic children.[1-4]

The use of multiple indexes of verbal/nonverbal functioning provided an internal replication of the correlational results and also ensured that the children—who varied greatly in their performance on these tasks—were adequately assessed. It is important to recognize that the verbal and nonverbal measures were correlated (r=.64 to .72) because of the influence of general intellectual factors,[1,2] which reduced the possibility of observing differences in the pattern of correlations with the MR imaging measures.

Magnetic resonance imaging was performed either on the same day as the cognitive testing or in the closest possible period for children who could not be scanned because of equipment or scheduling problems. The MR imaging was performed with a 1.5-T superconducting magnet (General Electric, Milwaukee, Wis). One sequence of sagittal and two sequences of axial images of the brain were obtained. The T_1 sagittal images were obtained by means of a spin-echo two-dimensional sequence with an echo time of 20 milliseconds and a pulse repetition time of 700 milliseconds. The T_1 axial images were obtained with the use of an echo time of 25 milliseconds and a pulse repetition time of 900 milliseconds. Proton-density and T_2 axial images were obtained with a multiecho spin-echo sequence using 30-millisecond (repetition time, 2000 milliseconds) and 80-millisecond (repetition time, 3000 milliseconds) echo times, respectively. For the T_1 sagittal, proton-density, and T_2 axial sequences, the slices were 5 mm thick and had a 2.5-mm interslice spacing. The T_1 axial slices were 3 mm thick and had a 1.0-mm interslice spacing. For quantitative measurement, films were reviewed to identify the most midline sagittal slice depicting the corpus callosum. In addition, each sagittal slice depicting the lateral ventricles in the right and left hemispheres was identified. The internal capsules (projection fiber) and the centra semiovale (association fiber) above the lateral ventricles were measured on T_2 axial images. Representative examples of these brain areas on MR images are presented in Figs 1 and 2.

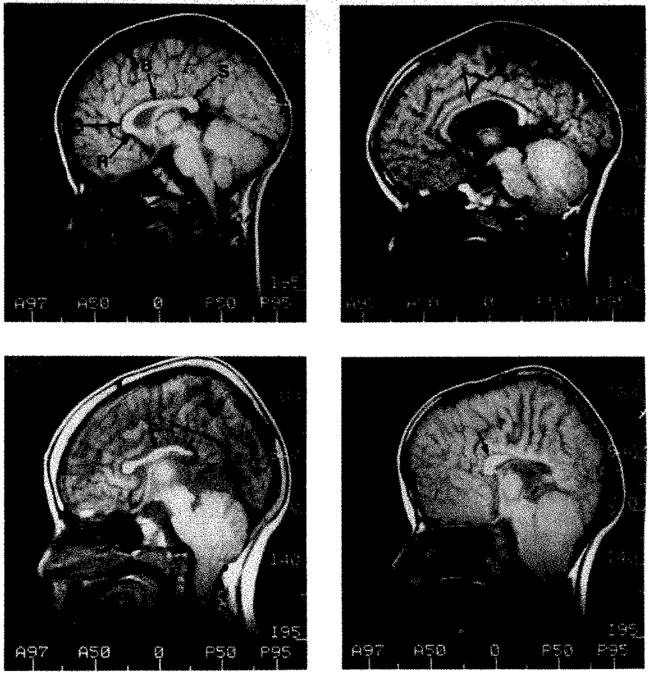

Fig 1.—*Neuropathologic abnormalities of the corpus callosum from midsagittal magnetic resonance images of children with hydrocephalus. Top left, Normal corpus callosum with arrows indicating the rostrum (R), genu (G), body (B), and splenium (S). Top right, The corpus callosum (arrow) is hypoplastic. Bottom left and right, Varying degrees of partial agenesis of the corpus callosum (arrows).*

Each of these slices was archived on tape and later reconstructed for measurement on a personal computer (386 IBM compatible) with the use of a program written specifically for this study. Several image-enhancing operations could be performed to highlight better a specific brain region for morphometric measurement. This included histogram equalization to use the full dynamic range of the monitor,[20] high-pass digital filtering (convolving the image with several edge detection template matrices), and low-pass filtering with the use of a local median computation.

Specific structures were measured by filling the specified structure to its boundaries with a preselected color. A region-filling algorithm was used to count the total number of pixels enclosed within these irregularly shaped boundaries.[21] For the corpus callosum, internal capsules, and centra semiovale, the cross-sectional area was quantitated. For the lateral ventricles, the volume in cubic millimeters was computed as the product of the cross-sectional area, slice thickness, and interslice spaces. To control for minor positional differences across scans, all measurements were made relative to the size of the brain or hemisphere depicted in a given slice. Generally, the small amount of freehand drawing required was necessary only to separate sinuses and cerebellum from brain/hemisphere computations. Since the highlighting of brain areas was automated, these measures were highly reliable and reproducible.

Two sets of statistical analyses were completed. The first set compared MR imaging measurements across the four groups of interest by means of repeated-measures analysis of variance (ANOVA) with post hoc comparison based on Tukey's Honestly Significant Difference method. The second set of analyses did not address group differences, but collapsed groups to correlate the MR imaging measurements with the six cognitive variables.

RESULTS

Means and SDs for the MR imaging ratio-based measurements are presented in Table 3. Sample sizes were re-

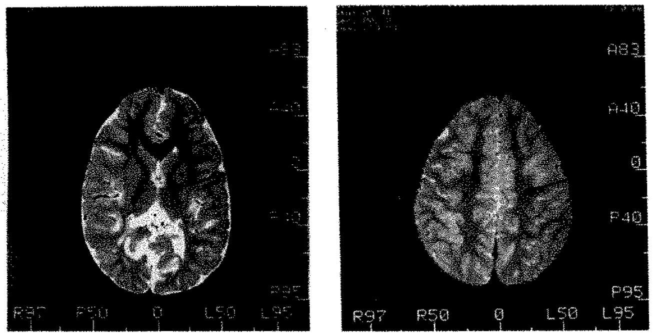

Fig 2.—*Cross-sectional areas from T_2 axial magnetic resonance images with arrows indicating the internal capsules (left) and centra semiovale (right) in the right and left hemispheres.*

duced for the MM and AS groups because in some cases the internal capsule and centrum semiovale could be visualized but could not be accurately quantitated because of movement artifact or shunt-related distortions.

The most significant finding involved the corpus callosum–whole brain ratio, which was smaller in MM and AS groups. The corpus callosum–whole brain ratio ANOVA yielded a significant effect of group ($F[3,40]=10.98$, $P<.0001$). Post hoc comparisons revealed no significant differences ($P<.05$) between the MM and AS groups. However, ratios in both groups were significantly smaller than those in both the M and normal groups ($P<.002$), which were not significantly different from each other.

The lateral ventricles were larger in all three patient groups. Repeated-measures ANOVA across groups revealed significant effect with asymmetric ventricles. The two SB groups and the AS group were not significantly different from each other, but all three differed significantly from normal subjects on both the right ($P<.002$) and left ($P<.002$) hemisphere ratios.

The internal capsules were smaller in all three patient groups. Repeated-measures ANOVA for internal capsule measures yielded a significant group effect for ratios with the right ($F[3,34]=3.67$, $P<.03$) and left ($F[3,34]=3.38$, $P<.03$) hemispheres. Significant differences were apparent on post hoc follow-up between the three clinical groups relative to the controls in both hemispheres (right, $P<.002$; left, $P<.003$). However, there were no significant asymmetries in the size of the internal capsule within these groups.

Centra semiovale measurements were more difficult to obtain because of the distortions of the images due to effects of hydrocephalus and the shunt-related skull defect. Because of effects of hydrocephalus, measures in the MM and M groups had to be taken near the vertex, whereas the shunt-related skull defects in the AS group mandated measurements at a deeper level. To deal with this problem, two sets of measurements were taken in the normal subjects to ensure comparability with the MM/M and AS groups. These data were analyzed separately, comparing data for the MM/M group with measures from the normal subjects taken nearer the vertex and those for the AS group with measures from the normal subjects taken at a deeper level. No significant group differences or interactions were present in either analysis ($P>.10$).

Table 4 presents means and SDs for the six cognitive measures standardized with a mean of 100 and SD of 15. To evaluate the hypothesis that the hydrocephalic groups would show lower nonverbal than verbal scores, each of the three sets of tasks was subjected to a repeated-measures ANOVA with group (four levels) as a between-subjects factor and task (two levels) as a within-subjects factor. All three resultant ANOVAs showed a significant group by task integration, as follows: McCarthy Scales, $F(3,39)=4.97$, $P<.006$; WISC-R, $F(3,36)=3.98$, $P<.02$; composites, $F(3,39)=2.66$, $P<.06$. Follow-up tests using Tukey's Honestly Significant Difference procedure for the McCarthy Scales and composites showed that the AS group had lower nonverbal than verbal scores relative to the other three groups ($P<.5$); for the WISC-R, both the AS and MM groups had lower nonverbal than verbal skills.

Fletcher et al[11] reported on a much larger study that included the children described in this article and additional causes of hydrocephalus, addressing the hypothesis of discrepancies in verbal and nonverbal functioning. They found a hydrocephalus by task interaction in which all hydrocephalic groups (irrespective of cause) had lower nonverbal than verbal scores. The difference between the present study and the study of Fletcher et al[11] is that the latter study was larger, had additional causes of hydrocephalus, and excluded children who did not have a Verbal IQ or Performance IQ above 70. The present study included children regardless of IQ level to avoid biasing the results by not fully accounting for severity of hydrocephalus. Two children with MM in this study with low IQ scores are missing from the WISC-R analysis because they could not complete all subtests, which is why the WISC-R scores show larger discrepancies in Table 4. Requiring children to have a Verbal or Performance IQ score above 69 is necessary for an adequate test of the discrepancy hypothesis because the relationship of Verbal IQ and Performance IQ changes with the overall level of intelligence as a property of test standardization.[2,11]

To address relationships of the MR imaging measurements and cognitive performance, each MR imaging measurement was correlated with the Verbal and Performance IQ from the McCarthy Scales and WISC-R and with the two composites. The centra semiovale data were not included because of the measurement difficulties and the absence of group differences in mean values. All subjects, including controls, were included to avoid truncation of the data distributions, which would have been present if only the patient groups were included.

As Table 5 shows, there were significant correlations between the corpus callosum–whole brain ratio and the McCarthy Scales and WISC-R Performance IQ scores, respectively, and the nonverbal composite. The correlations were lower and less robust for the three verbal measures. The right internal capsule–hemisphere ratio tended to correlate only with nonverbal measures. The left internal capsule–hemisphere ratio correlated significantly with both verbal and nonverbal scores and tended to correlate more highly with nonverbal measures.

Lateral ventricle–hemisphere correlations were not robust and were significant only for the left hemisphere with WISC-R Verbal IQ and for the right hemisphere with WISC-R Performance IQ. However, these correlations may be misleading because some children had asymmetric ventricles in opposite directions, such that averaging ratios may have obscured any relationships with skill discrepancies. To address this problem, difference scores were computed that represented the volume of the right minus left lateral ventricle–hemisphere ratios and WISC-R Verbal IQ minus Performance IQ. These difference scores correlated

Table 3.—Means and SDs for Magnetic Resonance Imaging Quantitative Measurements

	Spina Bifida			
Variable	**Meningomyelocele**	**Meningocele**	**Aqueductal Stenosis**	**Normal**
Corpus callosum, mm^2*				
Mean±SD	0.0299±0.0085	0.0489±0.0145	0.0376±0.0119	0.0500±0.0087
N	17	6	9	12
Lateral ventricle, mm^3				
Right†				
Mean±SD	0.0671±0.0546	0.0545±0.0544	0.0567±0.0505	0.0140±0.0059
N	17	6	9	12
Left‡				
Mean±SD	0.0864±0.0549	0.0572±0.0500	0.0589±0.0404	0.0167±0.0063
N	17	6	9	12
Internal capsule, mm^2				
Right‡				
Mean±SD	0.0278±0.0084	0.0289±0.0127	0.0256±0.0046	0.0388±0.0115
N	15	6	6	11
Left‡				
Mean±SD	0.0278±0.0107	0.0260±0.0157	0.0256±0.0083	0.0401±0.0122
N	15	6	6	11
Centrum semiovale, mm^2				
Right				
Mean±SD	0.2619±0.1198	0.2987±0.0936	0.3437±0.0399	0.2945±0.0836§ 0.3347±0.0978‖
N	14	6	6	12
Left				
Mean±SD	0.2718±0.1143	0.2681±0.0528	0.3600±0.0959	0.2864±0.0563§ 0.3398±0.0932‖
N	14	6	6	12

*$P<.0001$.

†$P<.03$.

‡$P<.005$.

§Measured comparably with the spina bifida group.

‖Measured comparably with the aqueductal stenosis group.

Table 4.—Means and SDs for Age and Cognitive Test Performance*

	Spina Bifida			
	Meningomyelocele	**Meningocele**	**Aqueductal Stenosis**	**Normal**
Age, y				
N	17	6	9	12
Mean±SD	86.64±6.56	88.40±6.28	90.45±10.88	90.65±5.39
McCarthy score				
N	17	6	9	12
Mean±SD				
Verbal	85.97±17.84	89.80±14.90	96.33±16.47	106.50±9.83
Perceptual-performance	83.58±19.19	100.60±13.82	82.83±18.48	113.13±12.94
WISC-R score				
N	15	6	8	12
Mean±SD				
Verbal	91.33±17.89	100.66±12.31	104.75±19.23	115.50±11.81
Performance	82.73±21.00	108.50±15.73	88.00±18.81	112.16±8.09
Cognitive composite				
N	17	6	9	12
Mean±SD				
Verbal	83.91±18.61	84.49±19.12	91.95±20.44	101.80±6.24
Nonverbal	80.55±14.64	92.98±8.11	81.01±11.97	100.66±10.49

*WISC-R indicates Wechsler Intelligence Scale for Children–Revised.

at .46 ($P<.03$). The relationship is plotted in Fig 3, which shows that children with significantly larger (ie, more pathologic) left ventricles had lower Verbal IQ and children with significantly larger (ie, more pathologic) right ventricles had lower Performance IQ.

Several supplemental analyses were conducted. Since assignment of groups as MM/M confounds treatment (shunting), data were also analyzed by collapsing across MM/M into shunt (N=16) and no shunt (N=7) groups. There were no changes in the pattern of results, including the size of the right lateral ventricles (shunt, 0.0560±0.0487; no shunt, 0.0817±0.0639) and left lateral ventricles (shunt,

Table 5.—Bivariate Correlations of Quantitative MR Imaging Measurements and Cognitive Performance in Children With Spina Bifida or Aqueductal Stenosis and Controls*

	Cognitive Test					
	McCarthy		WISC-R		Composites	
MR Imaging Variable	Verbal	Perceptual-Performance	Verbal	Performance	Language	Visual-Spatial
Corpus callosum/whole brain	.32†	.50‡	.38†	.54‡	.18	.47‡
N	44	44	41	41	44	44
Lateral ventricle/hemisphere						
Right	−.07	−.27	−.20	−.35†	.15	−.21
Left	−.18	−.24	−.31†	−.28	−.27	−.15
N	44	44	41	41	44	44
Internal capsule/hemisphere						
Right	−.12	.36†	.13	.41†	.12	.41†
Left	.35†	.45‡	.28	.43‡	.35†	.47‡
N	34	34	33	33	34	34

*MR indicates magnetic resonance; WISC-R, Wechsler Intelligence Scale for Children–Revised.
†$P<.05$.
‡$P<.01$.

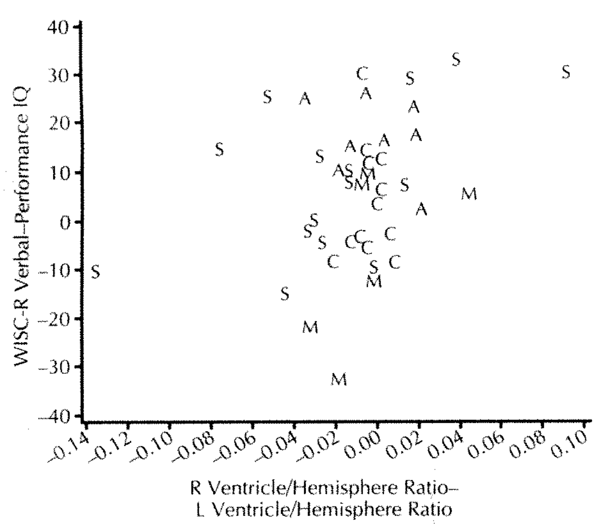

Fig 3.—*Plot of differences in lateral ventricle volumes against Wechsler Intelligence Scale for Children–Revised (WISC-R) Verbal IQ–Performance IQ differences for children with meningomyelocele (S), meningocele (M), aqueductal stenosis (A), and controls (C). Subjects in the lower left quadrant have larger left ventricles and lower Verbal IQ; subjects in the upper right quadrant have larger right ventricles and lower Performance IQ.*

0.0730±0.0463; no shunt, 0.0918±0.0709). The presence of a shunt in the right or left hemisphere was also analyzed in relation to the cognitive data to ensure that skill discrepancies were not related to side of shunting, with no significant group differences or interactions dependent on location of shunt ($P>.10$). Absolute measures of central nervous system structures correlated highly with the ratios. Correlations exceeded .86, with most above .90, so that similar results would have been obtained with absolute measures of the structures of interest.

COMMENT

In this study, children with congenital hydrocephalus showed measurable reductions in the size of two midline cerebral white-matter structures, the corpus callosum and the internal capsule. In the MM and AS groups, the corpus callosum was measurably smaller, supporting hypothesized reductions in the size of the commissural pathways. As expected, the lateral ventricles were larger in the MM and AS groups. An unexpected finding was the larger ventricle sizes in the M group. The explanation is that many of the children with M had mild hydrocephalus that did not require shunting. When shunts were used in the more severely hydrocephalic children, the end result was that the ventricles became comparable with those whose ventricular volume did not reach the size necessitating a shunt. The size of both the corpus callosum and the right internal capsule correlated positively and significantly with the nonverbal cognitive measures. There was also a tendency for the area of the left internal capsule to correlate better with nonverbal than verbal scores. However, only the MM and AS groups had both smaller corpora callosa and discrepancies in verbal and nonverbal functioning. These findings highlight the importance of white-matter structures, particularly the corpus callosum, for development of nonverbal cognitive skills.

Although hydrocephalus may physically impact the corpus callosum, the congenital agenesis of the corpus callosum may be part of the multiple abnormalities attributable to neuroembryogenesis.[5] However, hydrocephalus-related changes may also be related to skill discrepancies. The fact that lateral ventricle correlations were not particularly robust may be misleading, since only children with severe hydrocephalus received shunts. The size of the ventricles after shunting may therefore be a misleading index of the severity of hydrocephalus. In addition, children with significantly asymmetric ventricles did show reductions in either verbal or nonverbal cognitive skills corresponding with the larger ventricle (Fig 3). Perhaps more revealing are the internal capsule measures, which may well reflect the degree to which the brain was distended by hydrocephalus during crucial periods of myelination. Although these MR imaging–based measurements were not asymmetric, even the size of the left internal capsule correlated more highly with nonverbal cognitive performance. These findings are consistent with current hypotheses suggesting that the development of nonverbal cognitive skills is dependent on the integrity of the central nervous system white matter in both hemispheres, such that the hemisphere in which the lesion occurs is of less importance for white-matter lesions.

Corpus callosum abnormalities have not been emphasized in children with congenital hydrocephalus. When hypoplasia is included, most of the abnormalities in this study involved the splenium and degrees of the posterior body. The posterior body connects association areas involved in visual attention, sensorimotor integration, and other higher-order cortical functions; the splenium connects visual areas of the occipital lobes.[22] Since these children did not exhibit complete agenesis, they were unlike acallosal children whose cognitive deficits have been attributed to "crowding" due to bilateral representation of functions.[23] Also, since recent work has not demonstrated bilateral representation of function in acallosal children, who are generally lower in intellectual functioning than the children in this study, this explanation is less viable.[24]

Studies of the relationship of the corpus callosum and cognition suggest contradictory explanations for the cognitive discrepancies observed in hydrocephalic children. According to one view, the corpus callosum participates in hemispheric specialization by inhibiting information flow between the hemispheres, allowing each to prevail in a given function.[23] An alternative explanation is that the corpus callosum facilitates the interhemispheric transfer of information and functions in hemispheric activation and specialization.[24] This latter view is consistent with theories of hemispheric specialization in which the right hemisphere is more able to process novel stimuli and integrate intermodal information and the left hemisphere is more capable of unimodal processing and the storage of compact codes.[25] Consistent with this view, reductions in callosal pathways have been hypothesized to result in specific deficits in attention and other cross-modal functions, as well as language deficiencies associated with failure of the right hemisphere to specialize.[10,26] This study did not show these hypothesized specific language and attention deficits, but it demonstrated impairment of higher cortical functions commonly associated with the posterior parietal areas of the right hemisphere. These results imply a failure of such systems to develop because of reduced interhemispheric communication. The resulting lack of information would prevent normal specialization of the right hemisphere, consistent with a facilitatory model of the corpus callosum as well as with current theories of hemispheric specialization.[10,25]

Selective reductions in nonverbal cognitive functioning have also been observed in other childhood populations with disease-related neuropathologic changes in cerebral white matter, most notably patients with leukemia treated with central nervous system irradiation and children with severe closed head injuries.[1,10,27] Rourke[10] argued that the reduction in nonverbal cognitive skills in children with white-matter disorders reflects (1) inefficient interhemispheric communication and (2) reduced input-output of sensory and motor information due to disturbances of the corpus callosum and projection fiber pathways. This study supports both of these hypotheses.

It is also apparent that severity of hydrocephalus may interfere with the development of white-matter structures and both verbal and nonverbal skills. Similarly, hydrocephalic children can also have other central nervous system anomalies that influence development. Hence, an adequate understanding of the relationship of cognitive functioning and central nervous system neuropathologic characteristics in children with congenital hydrocephalus and other disorders involving the cerebral white matter will require more detailed measurements in larger samples of children. This article supports the value of morphometric analysis of specific neuroanatomic structures from MR imaging, in association with neuropsychological assessment, as a basis for these studies.

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Magnetic Resonance Imaging Signal Hyperintensities in the Deep and Subcortical White Matter

A Comparative Study Between Stroke Patients and Normal Volunteers

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• Mixed population studies suggest a relationship between deep and subcortical white matter hyperintensities on magnetic resonance imaging and cerebrovascular disease. To further clarify this issue we compared the prevalence and extent of such signal abnormalities between a group of 133 consecutive stroke patients (mean age, 54.7±16.7 years) and 101 normal volunteers (mean age, 54.7±13.1 years). Diabetes and cardiac disease were significantly more common in patients than in normal subjects. Prevalence rates of clinically silent lesions were 44% and 47.5%, respectively. Beginning confluent and confluent foci were seen in 19.5% of patients, but in only 7.5% of normal subjects. Significant univariate correlations were found for the presence and extent of lesions with age, diabetes, cardiac disease, severity of extracranial carotid arteriosclerosis, and arterial hypertension, but not with the diagnosis of stroke or the type of brain infarction. Multivariate regression analysis established age and diabetes mellitus as the only independent predictors of white matter damage. We conclude that more extensive white matter abnormalities in stroke patients stem from their higher rate of cerebrovascular risk factors but are unrelated to the occurrence of ischemic attacks per se.

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Magnetic resonance imaging (MRI) white matter hyperintensities (WMH) are a common finding in patients with various diseases,[1-6] but are also encountered in clinically asymptomatic individuals.[7-12]

Unlike periventricular caps and lining, which probably represent normal variants of periventricular water content,[9,13] hyperintensities in the deep and subcortical white matter have been repeatedly related to advanced age and risk factors for stroke. Therefore, many investigators suggested that these lesions are a subclinical form of ischemic leukoencephalopathy.[2,7,8,14-16] This is strongly supported by pathologic correlations[16-19] showing enlarged perivascular spaces, perivascular demyelination, and sometimes frank lacunar infarctions. In addition, some studies indicate a relationship between MRI white matter damage and a history of stroke.[2,15,20] This may lead to the assumption that the presence of white matter abnormalities in asymptomatic individuals allows to predict cerebrovascular accidents.

We tried to clarify this question by comparing the prevalence and extent of WMH between stroke patients and normal subjects, realizing that a population-based long-term study will ultimately be imperative.

Our aims were to determine any independent statistical association of WMH with cerebrovascular disease, and to establish a possible linkage with the type of brain infarction.

SUBJECTS AND METHODS

All inpatients of the Department of Neurology, Karl-Franzens University, Graz, Austria, with a diagnosis of stroke that had been referred to MRI during a 4-year period were enrolled. Normal subjects consisted of participants of a study on the prevalence of cerebrovascular risk factors in our community who were examined during the same time period. Data on subsets of this sample have been published elsewhere.[7-9]

Patients and normal subjects underwent thorough physical and neurologic examinations, repeated blood pressure readings, a standard laboratory screening, electrocardiogram, Duplex scanning of the extracranial cerebral arteries, and MRI.

Diagnosis of arterial hypertension (≥160 mm Hg systolic), diabetes mellitus (8.8 mmol/L fasting blood glucose level), and cardiac disease relied on the patients' history and appropriate laboratory test results.

Extracranial arterial disease was graded following a previously described 6-point scale[21] ranging from 0 (no atherosclerotic disease) to 5 (bilateral stenosis >70% or occlusions).

Magnetic resonance imaging was performed on a 1.5- Tesla supraconducting magnet using T2-weighted (TR/TE 2000 to 2500/30 to 60 milliseconds) sequences in the transverse orientation. T1-weighted images (TR/TE 600/30 milliseconds) were generated in the sagittal plane. Slice thickness was 5 mm and the matrix size used was 128×256 pixels. All images were read by one of us (F.F.) without knowledge of the clinical diagnosis. The scans were evaluated for WMH and areas of infarction. White matter hyperintensities were graded according to our scheme[8,9,22]: 0, absent; 1, punctate; 2, beginning confluent; and 3, confluent. Based on pathologic evidence for an ischemic origin of irregular periventricular hyperintensities (unpublished data), the latter were also considered as grade 3 WMH.

Infarct classification intended to reflect potential pathogenetic mechanisms.[23-25] Hence, they were categorized as territorial (thromboembolic), watershed (hemodynamic), and lacunar (microcirculatory) infarcts. Lacunes were focal lesions involving the basal ganglia, the internal capsule, the thalamus, or the brain stem not exceeding a maximum diameter of 10 mm. The Statistical Package of Social Sciences (SPSS/PC+) was used for database management and statistical analysis. The χ^2 test was applied to evaluate significant differences between frequency distributions. Differences of means between two groups were assessed by the Student *t* test. A one-way analysis of variance together with Duncan's *t* test was used to compare means of more than two subsets. To provide a univariate comparison of the WMH scores with clinical parameters, Pearson's correlation coefficient was applied for continous and the Mann-Whitney *U* test for discrete variables. A multivariate linear regression analysis was performed on the whole study cohort and its two subsets to assess the relative contribution of each parameter on the WMH score. Forward selection stepwise regression analysis was employed

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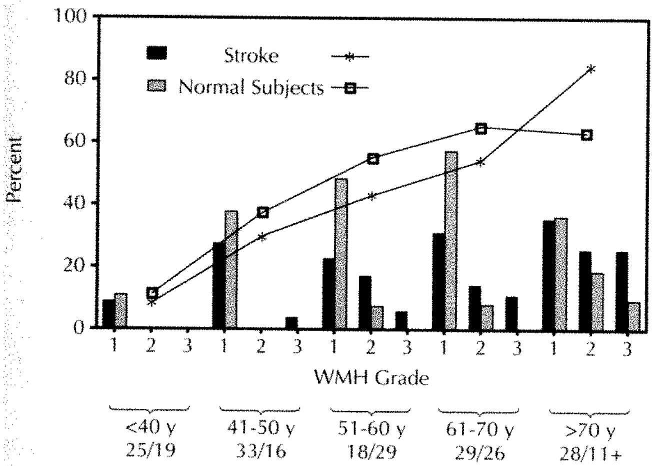
Table 1.—Demographic Data and Risk Factors

	Stroke	Normal Subjects	*P*
Patient No.	133	101	. . .
Age, y (mean±SD)	54.7±16.7	54.7±13.1	.97
Age range, y	18-90	31-84	. . .
Male:female	66:67	67:34	.01
No. (%)			
Hypertension	48 (36.1)	35 (34.7)	.82
Diabetes	27 (20.3)	11 (10.9)	.05
Cardiac disease	52 (39.9)	17 (16.8)	.003

Table 2.—Univariate Correlations Between Clinical Parameters and White Matter Hyperintensity Score

Parameter	Mean±SD	Prevalence, %	Test Statistic	*P*
Age, y	54.7±15.2	. . .	r=.58	.0001
Sonography score	1.3±1.4	. . .	r=.18	.01
Diabetes	. . .	16.2	z=4.69	.0001
Cardiac disease	. . .	29.5	z=3.90	.0001
Hypertension	. . .	35.5	z=1.95	.05
Stroke	. . .	56.8	z=0.61	.54
Sex, male	. . .	56.8	z=0.60	.54



Prevalence (percent) of white matter hyperintensities (WMH) within various age groups. Bars indicate percentage of grade 1 to 3 abnormalities. Line diagrams display overall frequency. Plus sign indicates number of stroke/normal subjects.

Table 3.—Multivariate Regression Analysis: Clinical Parameters and White Matter Hyperintensity Score

Parameter	B	SEB	β	T	*P*
Age	0.025	0.004	0.442	6.79	<.001
Diabetes	0.439	0.140	0.191	3.13	.002
Stroke	0.119	0.105	0.070	1.13	.25
Sex	0.042	0.099	0.025	0.42	.67
Sonography score	0.021	0.101	0.013	0.21	.83
Cardiac disease	0.004	0.033	0.004	0.127	.94
Hypertension	0.005	0.105	0.003	0.049	.96

Table 4.—White Matter Hyperintensity (WMH) and Infarct Type*

	Infarct Type, No. (%)		
	Territorial	Lacunar	Watershed
Patient No.	61	27	17
WMH grade			
1	15 (24.6)	8 (29.6)	4 (23.5)
2	7 (11.5)	4 (14.8)	4 (23.5)
3	4 (6.6)	1 (3.7)	0
WMH, total	**26** (42.6)	**13** (48.1)	**8** (47.0)

*χ^2 Test: differences not significant.

thereafter to create a model of significant independent predictors of white matter changes.

RESULTS

One hundred thirty-three patients with strokes and 101 normal subjects were included in this study. Both groups were comparable for age. There was a male preponderance among the normal subjects. Diabetes and cardiac disease were significantly more common in patients than in normal subjects (Table 1). Overall, 59 (44.4%) stroke patients and 48 (47.5%) normal subjects had WMH.

The Figure gives a breakdown of WMH prevalence among various age categories. The respective frequencies of WMH were not significantly different between the two investigational groups. Prevalence and extent of abnormalities increased with advancing age independent of the clinical diagnosis. A total of 26 patients (19.5%) had grade 2 or 3 WMH as opposed to only seven normal subjects (6.9%) (P<.03).

Univariate associations between clinical parameters and the white matter lesion score are presented in Table 2. Presence and extent of WMH significantly correlated with age, diabetes, cardiac disease, the sonographic score, and hypertension. There was no significant association, however, between WMH and the diagnosis of strokes.

Multiple linear regression analysis identified age and diabetes mellitus as the only significant and independent clinical predictors of WMH (Table 3). Using forward selection stepwise regression age entered first (β=0.52, SEB=0.003, P<.00001) and diabetes second (β=0.22, SEB=0.14, P<.001). No other variables entered the model. Isolated analysis of stroke patients and normal subjects revealed identical results.

Among the stroke group there were 105 patients who had a single infarct type. The mean age of patients with territorial lesions was 55.6 years as opposed to 53.7 years in patients with lacunar and 52.6 years in those with watershed infarcts. These differences were not statistically significant. Groups also showed similar risk factor distributions. As can be seen from Table 4 neither the prevalence nor the extent of WMH differed depending on the type of infarction.

COMMENT

This study revealed almost equal prevalence rates of WMH in stroke patients and normal subjects. Patients exhibited more extensive white matter damage. At first glance the latter finding appears to corroborate two previous investigations by Awad et al[2] and Sullivan et al.[20] These authors identified a history of ischemic stroke as predictive for the presence and severity of white matter lesions. However, a detailed analysis of our data, using multivariate statistics, failed to support such a conjunction. White matter hyperintensities were independently related only to age and to a lesser extent to diabetes mellitus. As a consequence, the more marked white matter involvement seen in our stroke patients must be attributed to their higher freqency of diabetes, but cannot be considered a stroke-related phenomenon. The discrepancy to Awad and coworkers'[2] and Sullivan and coworkers'[20] studies probably stems from differences in population selection criteria. Both previous investigations were retrospective and analyzed patients referred to MRI as part of their medical evaluation. They did not include a reference group of normal individuals and the reported frequencies of "incidental" WMH therefore might have been influenced by concomitant disease processes.

Our study also failed to establish an association of WMH with different types of infarction believed to herald specific mechanisms of cerebral ischemia. The lack of any conjunction with lacunar strokes was surprising, because arteriolosclerosis has been generally suggested as the most likely cause of WMH.[2,7,15-19]

As in this study age has been consistently found to be the most powerful predictor of WMH.[2,8,9,11,14,15,25,26] The majority of authors attributed a subordinate pathogenetic importance to cerebrovascular risk factors.[1,2,8,9-11,14,15] Their impact on lesion occurrence is emphasized by a study that compared age-matched groups of elderly normal subjects with various risk factor combinations.[7] The more risk factors a subject had the higher the likelihood of lesion detection. Thus far it remained undetermined, however, which risk factor(s) actually contribute to the evolution of WMH. Hypertension has been considered most often,[1,2,10,14,15] but there are also studies that suggested cardiac disease[1,8,26] and like our's, diabetes mellitus[27] as potential indicators of white matter damage. This inconsistency in results may originate from possible differences in risk factor severity and duration among study populations. Such quantitative parameters remained unappreciated by all previous investigations, including our own study.

The striking correlation of WMH with aging implies that other age-related causative factors than those held responsible for atherothrombotic brain infarction play an important role in the pathogenesis of MRI white matter foci. In fact, they may represent the sequela of age-related alterations of blood vessels, a hypothesis supported by the consistent perivascular location of WMH. Pathologic studies observed focally decreased permeability of small-vessel walls with advancing age.[28,29] Subsequent malnutrition of the adjacent tissue may result in focal demyelination, which is the most common substrate of WMH in the brains of elderly individuals.[19] Cerebrovascular risk factors may exert an additional unfavorable effect on such a mechanism.

Our study failed to uncover any statistical association of WMH with the diagnosis of stroke or any specific type of brain infarction. This strongly suggests that the presence of such abnormalities will probably not enable us to better assess stroke risk than can be expected from an elementary clinical evaluation of cerebrovascular risk factors alone.

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Neuropsychiatric Correlates of Cerebral White-Matter Radiolucencies in Probable Alzheimer's Disease

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• We evaluated the neuropsychological functions, rate of disease progression, and psychiatric characteristics of 22 patients with probable Alzheimer's disease in whom periventricular white-matter radiolucencies (PWMRs) were seen on the computed tomographic scan of the brain and compared them with 22 matched patients with Alzheimer's disease without PWMRs. Executive/attention, lexical/semantic, memory/learning, and visuospatial functions did not differ between the two groups at baseline or at the 1-year follow-up examination. The frequency of major depression, delusions, and hallucinations did not differ between the groups. However, patients with PWMRs had significantly higher Hachinski Rating scores at both visits and were more likely to develop cerebrovascular disease during follow-up than were controls with Alzheimer's disease. These preliminary results suggest that the presence of PWMRs is not associated with specific cognitive and psychiatric features or with an altered rate of progression of Alzheimer's disease but does predict the development of clinically significant cerebrovascular disease.

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Periventricular white-matter radiolucencies (PWMRs) surrounding the lateral cerebral ventricles are observed frequently by computed tomography (CT) among patients with Alzheimer's disease (AD).[1-11] In addition, PWMRs are frequently seen in nondemented elderly individuals[2,6,8,11,12] and are believed to be more characteristic of vascular-based dementia syndrome than of AD.[1,5,7,11,13] The term *leukoaraiosis*, or rarefaction of white matter, has been proposed for these periventricular changes as seen on CT scans,[14] and they are thought to be the same as the high-intensity periventricular white-matter lesions observed on T_2-weighted magnetic resonance imaging (MRI) scans.[4,7,10]

Both MRI and CT scans have shown that the frequency of PWMRs does not differ between patients with AD and healthy elderly individuals.[2,8,10,15] Their presence seems to correlate with increasing age,[1,6,9,15,16] the presence of risk factors for cerebrovascular disease,[1,3,4,9,11,12,16,17] reductions in cerebral blood flow,[6,16,17] and, in the case of demented patients, with increasing severity of dementia.[1,2,18] Neuropsychological studies of dementia using with vascular and AD-type cases have demonstrated that individuals with PWMRs were more impaired than were those without PWMRs in attention/motor speed tasks, learning and immediate recall, and problem-solving tasks.[4,19] In addition, patients with PWMRs have shown a greater frequency of blunt affect and apathy than those without PWMRs.[4] These findings have led some authors to suggest that patients with PWMRs exhibit a "frontal lobe deficit"[4] and meet the criteria for subcortical dementia secondary to a vascular process.[4,9,19]

In view of the apparent vascular origin of PWMRs and the resulting clinical syndrome, we asked whether these white-matter changes are associated with alterations in the neurologic, psychiatric, or neuropsychological components of the AD syndrome. The purpose of this study was to compare and contrast the neuropsychiatric characteristics of carefully selected patients with AD with PWMRs or without.

PATIENTS AND METHODS

Patients

We reviewed the clinical records and brain CT scans of 104 consecutive patients with the clinical diagnosis of probable AD[20] who entered into a longitudinal study of dementia from August 1983 to August 1988.

Each patient underwent an extensive evaluation, including medical, neurologic, psychiatric, social work/nursing, and neuropsychological examinations, as have been previously described.[21,22] All patients were fluent speakers of English before the onset of dementia. The clinical diagnosis of AD was reached after a careful review at a consensus conference by two neurologists and two psychiatrists.[23] None of these patients had significant signs of cerebrovascular disease, and those with a score greater than 4 on the Hachinski Rating (HR)[24] scale or evidence of possible infarction in two or more contiguous sections of the CT scan were excluded from the longitudinal cohort and thus from our study.

All scans were obtained at study entry with a scanner (model 9800, General Electric, Milwaukee, Wis) without contrast enhancement, with 5-mm cuts through the ventricular system and

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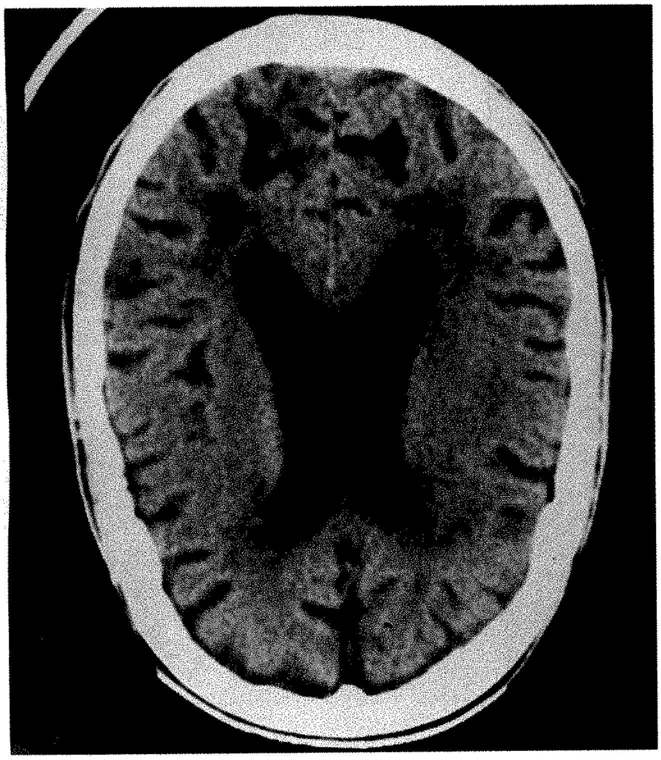

Computed tomographic scan showing periventricular white-matter radiolucencies around the frontal and occipital horns in a 68-year-old woman with a clinical diagnosis of probable Alzheimer's disease.

10-mm cuts above and below the ventricle system. Two neurologists (D.R. and O.L.L.) examined four white-matter regions from the right and left sides in four CT sections from each brain. An area was considered hypodense if its density fell between that of normal white matter and that of cerebrospinal fluid (Figure). The presence or absence of PWMRs was determined after the consensus of both neurologists. At the baseline examination, 31 (30%) of 104 patients had PWMRs. For this study, we selected 22 of these 31 patients with AD because they had at least two study visits and could be matched for age, duration of symptoms, and years of education with 22 patients with AD without PWMRs. The patients with PWMRs were considered "cases" and those without PWMRs were considered "controls." Demographic characteristics of the cases and controls are shown in Table 1.

Neuropsychological Assessment

A comprehensive battery of neuropsychological tests was administered to each subject at the time of entry into the study and 1 year later. Fifteen neuropsychological measures assessing four cognitive domains were selected for analysis: (1) memory: verbal[25] and face-name (Chadwick, unpublished data, 1992) paired associates, immediate recall of a figure,[26-28] and a short story[28]; (2) lexical/semantic: word generation,[29] Boston Naming Test,[30] and easy verbal paired associates[25]; (3) visuospatial: visual form discrimination,[31] figure copy,[26-28] three-dimensional block design,[31] and drawing tasks[30]; and (4) executive/attentional functions: Weigl's sorting task,[32] letter cancellation time,[33] verbal similarities,[34] trailmaking test,[35] and digit spans.[36]

Psychiatric Assessment

The psychiatric evaluations were conducted by board-certified psychiatrists using a semistructured interview[37] with patients and their primary caregivers. The diagnosis of syndromal major depression was made according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, (DSM-III-R)* criteria[38] at a subsequent chart review. Delusions were defined in accordance with the *DSM-III-R*[38] and were distinguished from confabulation, disorientation, and amnesia by requiring that the endorsement of false beliefs persisted despite contrary evidence. Auditory, visual, and olfactory hallucinations were accepted as present if the patients had spontaneously reported a sensory perception with no concomitant external perceptions. Details of the clinical criteria for diagnosis of depression, delusions, and hallucination have been described previously.[39,40] None of the patients in this study had a history of previous depression, psychotic illness, or substance abuse before the onset of dementia.

Table 1.—Demographic Data*

	Controls	Cases
Sex, F/M	14/8	16/6
Age, y	74.0±8.2	72.5±7.7
Educational level, y	13.0±3.1	13.0±3.3
Duration of symptoms, y	3.9±1.9	3.7±1.5

*Values are mean±SD.

Statistical Analysis

Because of the one-to-one case-control matching, we utilized a within-subject design for all analyses. Analysis of variance was used to evaluate changes over time, and McNemar's test for paired categorical data was used to analyze contingency tables. All tests of statistical significance are two-tailed, unless otherwise noted.

RESULTS

The patients were matched for age, educational level, and duration of symptoms of dementia, and there were no significant differences in Mini-Mental State Examination[41] scores ($t[21]=1.37$) and Blessed Rating scale[42] scores for activities of daily living ($t[21]=0.87$). There was a statistically significant difference between groups on the baseline HR scale[24] score ($t[21]=-2.19$, $P=.03$) (Table 2). At the follow-up visit, three cases (14%), but none of the controls, had HR scale scores greater than 4. An overall significant difference between groups ($F[1,21]=13.92$, $P<.001$) and a significant group-by-time interaction ($F[1,21]=12.65$, $P<.001$) were detected, reflecting the rise of HR scores among cases but not controls.

At the baseline examination, 10 cases (45%) and nine controls (41%) reported hypertension, ischemic heart disease, or both (cerebrovascular disease risk factors) (Table 3); none had diabetes mellitus. The diagnosis of ischemic heart disease required a history of documented myocardial infarction or an electrocardiogram indicating the presence of ischemic changes or arrhythmias. There was a trend toward a greater prevalence of diagnosed hypertension among the cases ($\chi^2=3.1$, $P=.07$), but the mean systolic and diastolic blood pressures (BPs) at baseline did not differ between cases and controls (systolic BP: $t[21]=0.96$, $P=.3$; diastolic BP: $t[21]=1.14$, $P=.2$). However, at the follow-up examination, the mean systolic BP of the cases was significantly higher than that of controls ($t[21]=2.71$, $P=.01$), although the mean diastolic BP did not differ between the two groups ($t[21]=0.81$, $P=.4$). Four of the cases with hypertension were taking antihypertensive medication at baseline and follow-up (three were taking β-blockers and one was taking diuretics), and two were taking antithrombotic medications. Two controls were receiving treatment with diuretics at baseline and follow-up.

The signs and symptoms outlined in the HR scale are presented in Table 4. There was a trend toward a greater frequency of focal neurologic symptoms among the cases

Table 2.—Cognitive, Activities of Daily Living, and Vascular Dementia Risk Measures in Cases and Controls*

	Baseline		Follow-up		F(*df*=1,21)		
	Cases	Controls	Cases	Controls	Group	Visit	Interaction
Mini-Mental State Examination score	18.5±4.3 (26-10)	20.3±6.0 (25-10)	14.9±6.0 (23-3)	16.5±6.0 (22-6)	1.47	0.22†	0.09
Blessed Rating	6.7±4.0 (1-13)	6.5±3.5 (0-14)	7.5±4.3 (2-15)	8.8±3.9 (3-18)	0.43	13.94†	1.36
Hachinski Rating	2.0±2.3 (0-4)	1.4±0.8 (0-3)	2.5±1.7 (0-8)	1.1±0.6 (0-2)	13.92†	2.78	12.65†

*Values are mean±SD (range) unless otherwise stated.
†*P*<.001.

Table 3.—Cerebrovascular Risk Factors

	Cases	Controls
Hypertension, No. (%)	8 (36)	2 (9)
Systolic blood pressure, mean±SD		
V1	142.9±23.9	136.6±18.6
V2*	142.9±19.3	126.8±18.3†
Diastolic blood pressure, mean±SD		
V1	84.5±9.5	81.4±8.5
V2*	82.0±9.4	79.2±10.8
Ischemic heart disease, No. (%)	3 (14)‡	7 (32)

*Blood pressure was available for 19 patients at follow-up.
†*t* Test, *P*<.05.
‡One patient had concomitant hypertension.

(χ^2=2.25, *P*=.06), and five (23%) of the cases had clear evidence of cerebrovascular disease at follow-up; none of the controls developed these features (χ^2=3.2, one-tailed *P*=.035). The five cases with cerebrovascular disease at the follow-up examination were as follows: (1) A 79-year-old hypertensive man had an episode of confusion followed by a right-sided face and arm paresis. Hypertension was labile, and no medication was administered to control BP. The autopsy of this patient revealed "definite AD,"[20] small left-sided temporal and left-sided superior parietal hemorrhagic infarcts, and cerebral amyloid angiopathy. (2) A 69-year-old hypertensive man developed unstable gait, abnormal results of primary sensory testing, unilateral cerebellar signs, asymmetric deep tendon reflexes, and episodes of dizziness with frequent falls. No evidence of cardiac arrhythmia was noted. The CT scan of the brain showed no focal abnormalities. He was not taking antihypertensive medication. (3) A 63-year-old woman with no cerebrovascular risk factors developed episodes of left-sided face and arm numbness and tingling sensation, left-sided extinction on double simultaneous stimulation, dressing apraxia, and unilateral cerebellar signs. The CT scan of the brain showed no focal abnormalities. (4) A 78-year-old man with no cerebrovascular risk factors reported two episodes of transient ischemia between visits. He had episodes of blurred vision and slurred speech followed by loss of consciousness lasting 1 to 4 minutes. The CT scan at that time showed a small infarct in the left caudate nucleus. At follow-up, he had unstable gait and episodes of dizziness. (5) An 86-year-old hypertensive woman with ischemic heart disease had three episodes of loss of consciousness between visits. No evidence of cardiac arrhythmia was noted, and no focal signs and symptoms were observed at follow-up. However, the CT scan obtained at follow-up showed several lacunar infarcts in the basal banglia and an infarct in the right parietal lobe. She was treated with β-blockers.

Twelve cases and seven controls underwent a third follow-up examination at the clinic. Two additional cases exhibited focal neurologic signs, and none of the controls developed cerebrovascular disease. Sixteen cases and 14 controls were followed up via repeated telephone interviews with the primary caregiver. The mean (±SD) follow-up time was 51.9±16.9 months. Twelve cases and six controls were institutionalized. No difference in rate of institutionalization was observed between the groups (χ^2=1.4, *P*=.22). Nevertheless, six cases and one control were confined to a wheelchair before institutionalization. Fifteen of the 44 patients have since died (seven cases and eight controls); nine of these 15 (three cases and six controls) were autopsied, and all had a pathologic diagnosis of "definite AD."[21] No difference in the mortality rate was observed between the groups (χ^2=.1, *P*=.75).

Psychiatric Symptoms

Three cases (14%) and four controls (18%) met the *DSM-III-R* criteria for syndromal major depression at baseline. Each of these patients was taking antidepressant medication at the time of both evaluations. Two cases were still depressed at the second visit and continued to receive the same medication. One additional case developed depression after the baseline examination. Three controls were still depressed at the follow-up visit. There was no significant difference between the groups in the frequency of major depression at baseline (χ^2=0, *P*=1) or follow-up (χ^2=.16, *P*=.61).

Delusions were reported in one case (5%) and in five controls (23%) at the baseline examination, all of which were paranoid delusions. Seven cases (32%) and five controls (23%) had delusions at the follow-up visit. There were no significant differences between the groups in the frequency of delusions at baseline (χ^2=2.25, *P*=.13) or follow-up (χ^2=.8, *P*=.37). Five patients (23%) in each group reported auditory and visual hallucinations at the baseline examination. Four cases (18%) and six controls (27%) had hallucinations at the follow-up examination. There was no significant difference between the groups in the frequency of hallucinations at baseline (χ^2=.12, *P*=.72) or follow-up (χ^2=.12. *P*=.72). Three cases (14%) and five controls (23%) had both delusions and hallucinations. Four cases and three controls were taking antipsychotic medication.

Neuropsychological Performance

From the larger battery of neuropsychological tests, data were selected to represent memory, visuospatial, lexical/

Table 4.—Ischemic Score Items in Cases and Controls at Baseline and Follow-up*

	Cases		Controls	
	Visit 1	Visit 2	Visit 1	Visit 2
Abrupt onset	0 (0)	1 (5)	0 (0)	0 (0)
Stepwise deterioration	0 (0)	2 (9)	0 (0)	0 (0)
Fluctuating course	0 (0)	0 (0)	0 (0)	0 (0)
Nocturnal confusion	0 (0)	3 (14)	0 (0)	0 (0)
Relative preservation of personality	14 (65)	11 (52)	12 (56)	9 (39)
Depression†	3 (14)	3 (14)	4 (18)	3 (14)
Somatic complaints	1 (5)	1 (5)	0 (0)	0 (0)
Emotional incontinence	1 (5)	2 (9)	2 (9)	1 (5)
History of hypertension	8 (36)	8 (36)‡	2 (9)	2 (9)
History of strokes	0 (0)	1 (5)	0 (0)	0 (0)
Evidence of associated atherosclerosis	10 (45)	10 (45)	9 (41)	9 (41)
Focal neurologic symptoms	0 (0)	4 (18)‡	0 (0)	0 (0)
Focal neurologic signs	0 (0)	3 (14)	0 (0)	0 (0)

*Values are number (percent).

†Criteria for major depression according to *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.*

‡$P>.05$.

semantic, and executive/attentional functions. The individual tests were grouped into these domains based on previously published factor analyses in patients with AD.[21,43] Performance on the battery of tests, including digit spans (forward and backward) and the Trailmaking Test, are shown in Table 5. Analyses of these data revealed no significant differences between cases and controls on any measure ($P>.05$ for all). Table 5 also presents the scores of 103 nondemented elderly individuals.[43]

Because all of the subjects could not provide reliable data at follow-up, detailed evaluation with all of these measures was possible with only 19 pairs of patients (eg, Trailmaking Test, part B). Table 6 presents the individual test data from those 19 pairs of patients who were able to provide follow-up data. There were no significant differences between the cases and controls on any of these measures ($P>.05$ for all). Summary measures of mental status revealed no significant differences in the rate of decline between the cases and controls. An analysis of variance of Mini-Mental State Examination scores revealed a significant decrease in scores over time (F[1,21]=47.22, $P<.001$). There was no significant difference between groups (F[1,21]=1.45, $P=.24$), and no interaction between groups and visits (ie, baseline to follow-up) (F[1,21]=.09, $P=.7$). There was no significant difference between groups on Blessed Rating scale scores (F[1,21]=.52, $P=43$) and no interaction between groups and visits (F[1,21]=1.36, $P=.25$).

COMMENT

We longitudinally examined the neuropsychiatric characteristics of a highly selected group of patients with AD whose CT scan of the brain revealed PWMRs. Patients with AD with PWMRs could not be differentiated from those without PWMRs by their presenting pattern of neuropsychological impairment, psychiatric symptoms, or rate of cognitive decline. However, patients with AD with PWMRs had higher HR scale scores at both visits and had a greater frequency of clinically significant cerebrovascular disease at the 1-year follow-up examination.

In nondemented middle-aged and elderly individuals and in demented elderly patients, PWMRs have been associated with cerebrovascular risk factors, especially hypertension.[1,3,4,8,9,11,16,17] In the present study, the proportion of patients with cerebrovascular risk factors was similar in both groups. However, mild hypertension was somewhat more frequent in patients with AD with PWMRs, and the mean systolic BP at follow-up was higher among patients with PWMRs, although this latter observation was due to a reduction of systolic BP among the patients without PWMRs rather than a rise among the patients with PWMRs. This partial discrepancy with previous reports may be based on the subjects surveyed and sampling methods. Patients selected for this longitudinal study were carefully evaluated by strict multidisciplinary clinical criteria; patients with other disease processes that could produce dementia were excluded. In addition, patients with hypertension, diabetes mellitus, and ischemic heart disease were excluded when the disease was severe and not well controlled. Despite these efforts to reduce potential causes that can affect the reliability of the clinical diagnosis, patients with AD with PWMRs had a greater risk for a vascular component to their dementia, as measured by the HR scale. Moreover, patients with AD with PWMRs had a greater frequency of cerebrovascular disease than did patients without PWMRs at the 1-year follow-up examination.

Although the mean HR scale scores were significantly different between the groups at both visits, questions may arise regarding the discrepancy between the number of patients with HR scale scores greater than 4 at the follow-up examination (n=3) and the number of patients who developed cerebrovascular disease (n=5). The absence of codable focal neurologic signs (patients 4 and 5) and symptoms (patient 5) may explain, in part, this discrep-

Table 5.—Performance on Selected Neuropsychological Tests in 22 Pairs of Patients at Baseline Evaluation*

	Controls	Cases	Healthy Elderly
Memory			
Story recall	1.61 (1.3)	2.07 (1.7)	7.43 (2.6)
Figure recall	6.27 (4.8)	5.74 (5.0)	20.0 (3.3)
Verbal paired associates (hard)†	30.4 (4.4)	28.7 (5.5)	14.4 (5.5)
Face-name paired associates†	25.6 (8.8)	24.9 (8.9)	12.4 (1.1)
Visuospatial			
Form discrimination	22.3 (8.7)	22.7 (6.2)	29.8 (2.2)
Block construction	32.1 (15.0)	34.4 (10.5)	43.1 (2.1)
Drawing tasks	13.0 (3.6)	12.7 (2.6)	16.3 (1.3)
Figure copy	18.7 (7.4)	17.8 (5.5)	23.5 (0.94)
Lexical-semantic			
Confrontation naming	25.1 (9.5)	23.4 (8.9)	38.6 (2.8)
Verbal fluency	8.63 (3.9)	7.19 (3.8)	14.2 (4.7)
Easy verbal paired associates	15.6 (8.0)	14.9 (6.8)	9.35 (0.93)
Executive/attention			
Verbal similarities‡	6.22 (3.8)	4.90 (3.4)	11.3 (1.1)
Weigl sorting‡	6.62 (4.6)	6.00 (2.6)	12.0 (1.9)
Letter cancellation†‡	115.2 (52.8)	118.7 (49.8)	66.5 (16.8)
Digits forward	5.86 (1.0)	5.19 (1.2)	6.99 (1.2)
Digits backward	4.09 (1.6)	3.43 (1.0)	5.53 (1.5)
Trailmaking†			
Part A	113.2 (77.2)	116.4 (61.1)	39.1 (13.8)
Part B	213.8 (41.1)	232.4 (21.31)	90.6 (38.9)

*Values are mean (SD).

†Time or error score; higher scores indicate poorer performance.

‡Used in executive composite scores.[43]

Table 6.—Performance on Selected Neuropsychological Tests in 19 Pairs of Patients at Follow-up*

	Controls	Cases
Memory		
Story recall	2.14 (1.7)	1.45 (1.4)
Figure recall	2.76 (2.9)	2.75 (3.6)
Verbal pairs associates (hard)†	31.3 (2.8)	32.7 (1.2)
Face-name paired associates†	30.5 (9.8)	31.0 (9.7)
Visuospatial		
Form discrimination	18.8 (10.7)	16.9 (10.0)
Block construction	25.6 (18.5)	21.1 (16.6)
Drawing tasks	12.0 (3.9)	10.0 (3.0)
Figure copy	15.1 (9.0)	10.8 (8.3)
Lexical/semantic		
Confrontation naming	20.1 (10.1)	15.5 (9.2)
Verbal fluency	9.8 (7.3)	7.1 (5.5)
Easy verbal pairs associates	19.9 (9.1)	18.8 (8.2)
Executive/attention		
Verbal similarities	4.14 (3.4)	3.18 (3.0)
Weigl sorting	5.55 (4.4)	5.50 (4.3)
Letter cancellation†	129.3 (60.1)	166.3 (71.0)
Digits forward	5.62 (1.6)	5.19 (1.5)
Digits backward	3.34 (1.8)	2.81 (1.5)
Trailmaking†		
Part A	132.9 (80.0)	162.4 (83.7)
Part B	222.0 (39.8)	237.1 (12.5)

*Values are mean (SD).

†Time or error score; higher scores indicate poorer performance.

ancy. In addition, the presence of infarcts on the CT scans of the brain that were only visible on a single 5-mm section were not interpreted as "strokes" by the clinicians.

All of the patients in this study met the diagnostic criteria for probable AD. Their mental status was clearly abnormal at study entry and became more impaired during the follow-up period. However, the presence of PWMRs was an indication of an underlying cerebrovascular disease that only became clinically apparent at the follow-up examination. In addition, patients with AD with PWMRs tended to be institutionalized earlier (12 cases vs six controls) and to develop early physical limitations, as indicated by the use of wheelchairs (six cases vs one control), although no statistical differences were observed. Consistent with previous observations,[44] no differences were noted in the natural history of patients with AD with and without PWMRs.

Neuropsychological studies in elderly demented patients have demonstrated slowness of thought, reduced motor speed/attention, deficits in learning, and memory and problem-solving difficulties.[4,19] These observations, and their relationship to cerebrovascular factors, led some authors to suggest that demented patients with PWMRs exhibit a variety of subcortical dementia, such as "subcortical arteriosclerotic encephalopathy" or Binswanger's disease. However, as noted previously,[45] studies that addressed the possible association between PWMRs and Binswanger's disease did not categorize patients by specific groups but rather grouped patients by the presence or absence of PWMRs.[4,19] These groups, therefore, contained not only patients with AD but also patients with vascular dementia and nondemented individuals. The strict selection criteria we used in patient selection permitted the examination of the clinical significance of PWMRs in relative isolation. We were unable to identify any difference between patients with AD with and without PWMRs in terms of their presenting pattern of neuropsychological defects, despite the variety of measures evaluated. These patients were matched in terms of duration of cognitive symptoms as well as age and education but not in terms of initial degree of cognitive dysfunction. Therefore, these findings strengthen the concept that patients with AD with and without PWMRs are not different neuropsychologically. By contrast, recent work by Diaz et al[46] has suggested that patients with AD with leukoaraiosis were more cognitively impaired than were those without leukoaraiosis. However, Diaz et al based their study on a limited and simplified neuropsychological examination, and the groups did not differ in terms of their performance of attentional tasks.

Elderly demented patients with PWMRs have been reported to show a greater frequency of apathy and blunt affect compared with those patients without PWMRs.[4] In addition, elderly patients with a diagnosis of major depression and dementia syndrome of depression have been reported to show a greater frequency and severity of PWMRs compared with healthy elderly individuals.[47,48] Our results, however, indicate that major depression and psychotic symptoms (eg, delusions and hallucinations) were not related to the presence of PWMRs in patients with AD. These findings are consistent with those of Harrell et al,[45] who found no relationship between high-intensity signals on MRI scans and depression in patients with AD.

Because this study was based on CT scan findings, it may raise some questions about whether this method is sufficiently sensitive to evaluate the cerebral white-matter lesions frequently observed in patients with AD. Current research studies favor the use of MRI. However, CT and MRI have different strengths and weaknesses. Both methods seem to detect large lesions that reflect demyelinization, loss of axons, and gliosis[2-4,8] known to be involved in the clinical correlates of PWMRs. However, CT cannot detect the small abnormalities that MRI can detect. As noted by Janota et al,[3] these are more heterogeneous and do not necessarily permit differentiation among the various pathologic entities underlying the abnormalities it reveals.[49-51] While not denying the usefulness of MRI, we suggest that CT is still a useful method to evaluate clinical radiologic correlations in dementia.

Our results indicate that PWMRs do not contribute to the clinical presentation of AD. However, we found that a vascular factor was associated with PWMRs in AD, as indicated by the HR scale and the development of cerebrovascular disease. We do not favor the hypothesis that this pattern represents Binswanger's disease. Rather, we view these white-matter changes as an independent pathologic entity that can be present without other cerebrovascular risk factors and can coexist with AD. While these results are clearly preliminary, the fact that the only patients to develop cerebrovascular disease were those with PWMRs strongly suggests that a large-scale study is warranted and that prophylaxis for the development of cerebrovascular disease should be considered.

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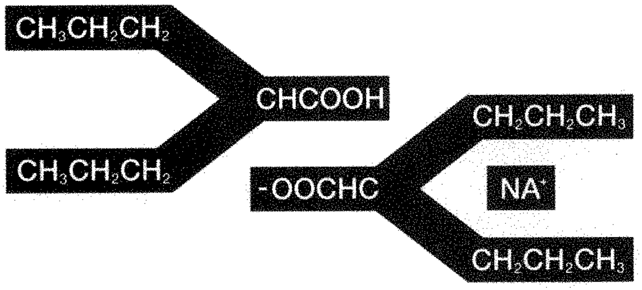

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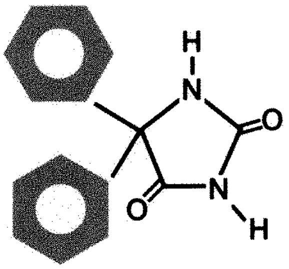

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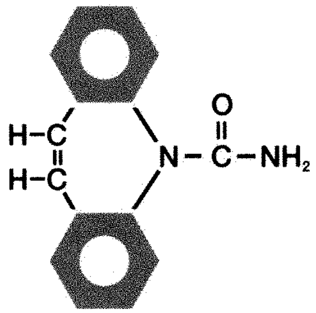

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ELAYED-RELEASE TABLETS

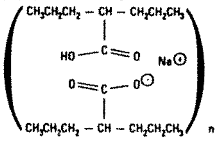
WARNING:

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTI-CONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF SEIZURE CONTROL SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

ESCRIPTION

ivalproex sodium is a stable co-ordination compound comprised of sodium valproate and lproic acid in a 1:1 molar relationship and formed during the partial neutralization of lproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as dium hydrogen bis(2-propylpentanoate). Divalproex sodium has the following structure:



ivalproex sodium occurs as a white powder with a characteristic odor.

DEPAKOTE tablets and Sprinkle capsules are antiepileptics for oral administration. EPAKOTE Sprinkle capsules contain specially coated particles of divalproex sodium uivalent to 125 mg of valproic acid in a hard gelatin capsule. DEPAKOTE tablets are pplied in three dosage strengths containing divalproex sodium equivalent to 125 mg, 0 mg, or 500 mg of valproic acid.

ctive Ingredients

5 mg Sprinkle capsules: cellulosic polymers, D&C Red No. 28, FD&C Blue No. 1, latin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.

DEPAKOTE tablets: cellulosic polymers, diacetylated monoglycerides, povidone, egelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, and vanillin.

In addition, individual tablets contain:
125 mg tablets: FD&C Blue No. 1 and FD&C Red No. 40.
250 mg tablets: FD&C Yellow No. 6 and iron oxide.
500 mg tablets: D&C Red No. 30, FD&C Blue No. 2, and iron oxide.

INICAL PHARMACOLOGY

valproex sodium is an antiepileptic agent which dissociates to the valproate ion in the strointestinal tract. The mechanism by which valproate exerts its antiepileptic effects has t been established. It has been suggested that its activity is related to increased brain lev- of gamma-aminobutyric acid (GABA).

Equivalent oral doses of DEPAKOTE (divalproex sodium) products and DEPAKENE lproic acid) capsules deliver equivalent quantities of valproate ion systemically. However, the rate of valproate ion absorption may vary with the conditions of use (eg, fasting postprandial) and the method of administration (eg, whether the contents of the capsule sprinkled on food or the capsule is taken intact).

When subjects are in a fasting state, peak plasma concentrations of valproate ion are served approximately 3 to 4 hours following administration of all DEPAKOTE products.

Experiments indicate that feeding can influence the rate of systemic absorption of valoate. In studies in which the contents of DEPAKOTE (divalproex sodium) Sprinkle capes were sprinkled on applesauce, feeding was found to delay the time to peak plasma ncentration by approximately 1.5 hours.

Compared to DEPAKOTE tablets, however, DEPAKOTE Sprinkle capsules (in the ting state) exhibit a slower rate of absorption, resulting in lower peak plasma concentrans (ie, fluctuations between minimum and maximum plasma valproate concentrations attenuated).

While absorption rate from the G.I. tract and fluctuation in valproate plasma concentrans vary with dosing regimen and formulation, the efficacy of valproate in chronic use is affected. Experience employing dosing regimens from once-a-day to four-times-a-day, well as studies in primate epilepsy models involving constant rate infusion, indicate that al daily systemic bioavailability (extent of absorption) is the primary determinant of zure control and that differences in the ratios of plasma peak to trough concentrations ween valproate formulations are inconsequential from a practical clinical standpoint.

Accordingly, coadministration of oral valproate products with food and substitution ong the various DEPAKOTE and DEPAKENE formulations should cause no clinical blems (see DOSAGE AND ADMINISTRATION). Nonetheless, any changes in dosage ministration, or the addition or discontinuance of concomitant drugs should ordinarily accompanied by close monitoring of clinical status and valproate plasma concentrans.

The plasma half-life of valproate is typically in the range of 6 to 16 hours. Half-lives in lower part of the range are usually found in patients taking other antiepileptic drugs able of enzyme induction.

Valproate is primarily metabolized in the liver. The major metabolic routes are gluronidation, mitochondrial beta oxidation, and microsomal oxidation. The major metaboes formed are the glucuronide conjugate, 2-propyl-3-keto-pentanoic acid, and ropyl-hydroxypentanoic acids. Other unsaturated metabolites have been reported. The jor route of elimination of these metabolites is in the urine.

Patients on monotherapy will generally have longer half-lives and higher concentrans of valproate at a given dosage than patients receiving polytherapy. This is primarily to enzyme induction caused by other antiepileptics, which results in enhanced clearce of valproate by glucuronidation and microsomal oxidation. Because of these changes valproate clearance, monitoring of antiepileptic concentrations should be intensified enever concomitant antiepileptics are introduced or withdrawn.

The therapeutic range is commonly considered to be 50 to 100 mcg/mL of total valate, although some patients may be controlled with lower or higher plasma concentrans.[5] Valproate is highly bound (90%) to plasma proteins in the therapeutic range; wever, protein binding is concentration-dependent and decreases at high valproate contrations. The binding is variable among patients and may be affected by fatty acids or by hly bound drugs such as salicylate. Some clinicians favor monitoring free valproate contrations, which may more accurately reflect CNS penetration of valproate. As yet, a consus on the therapeutic range of free concentrations has not been established; however, nitoring total and free valproate may be informative when there are changes in clinical tus, concomitant medication, or valproate dosage.

ICATIONS AND USAGE

PAKOTE (divalproex sodium) is indicated for use as sole and adjunctive therapy in the atment of simple and complex absence seizures, and adjunctively in patients with multi seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciouss accompanied by certain generalized epileptic discharges without other detectable ical signs. Complex absence is the term used when other signs are also present.

SEE WARNINGS FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNC-N.

NTRAINDICATIONS

VALPROEX SODIUM SHOULD NOT BE ADMINISTERED TO PATIENTS WITH PATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the g.

RNINGS

patic failure resulting in fatalities has occurred in patients receiving valproic acid. se incidents usually have occurred during the first six months of treatment. Seri or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of ure control, malaise, weakness, lethargy, facial edema, anorexia, and vomiting. ients should be monitored closely for appearance of these symptoms. Liver func tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKOTE products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risks. Above this age group, experience has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage in Pregnancy: ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.[1]

OTHER CONGENITAL ANOMALIES (EG, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TOCONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

ANIMAL STUDIES ALSO HAVE DEMONSTRATED VALPROATE INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

PRECAUTIONS

Hepatic Dysfunction: See BOXED WARNING, CONTRAINDICATIONS AND WARNINGS.

General: Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (eg, low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. Asymptomatic elevations of ammonia are more common and when present require more frequent monitoring. If clinically significant symptoms occur, DEPAKOTE therapy should be modified or discontinued.

Since valproate may interact with concurrently administered antiepileptic drugs, periodic plasma concentration determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See DRUG INTERACTIONS).

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Information for Patients: Since DEPAKOTE products may produce CNS depression, especially when combined CNS depressants (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

The specially coated particles in DEPAKOTE Sprinkle capsules have been observed in the stool, but this occurrence has not been associated with clinically significant effects.

Drug Interactions: Valproate may potentiate the action of CNS depressants (ie, alcohol, benzodiazepines, etc).

The concomitant administration of valproate with drugs that exhibit extensive protein binding (eg, aspirin, carbamazepine, dicumarol, and phenytoin) may result in alteration of serum drug concentrations.

There is evidence that valproate can cause an increase in serum phenobarbital concentrations by impairment of nonrenal clearance. This phenomenon can result in severe CNS depression. The combination of valproate and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone is metabolized to a barbiturate and, therefore, may also be involved in a similar or identical interaction.

There have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. Most reports have noted a decrease in total plasma phenytoin concentration. However, increases in total plasma phenytoin concentration, however, increases in total phenytoin serum concentration have been reported. An initial fall with subsequent increase in total phenytoin concentrations has also been reported. In addition, a decrease in total serum phenytoin with an increase in the free vs. protein bound phenytoin concentrations has been reported. The dosage of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide concentrations. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Caution is recommended when valproate is used with drugs affecting coagulation (eg, aspirin, warfarin). See ADVERSE REACTIONS.

Evidence suggests that there is an association between the use of certain antiepileptics and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing antiepileptics effectively lower plasma concentrations of the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. While valproate is not a significant enzyme inducer, and, therefore, would not be expected to decrease concentrations of steroid hormones, clinical data about the interaction of valproate with oral contraceptives is minimal.[2]

Carcinogenesis: Valproic acid was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 80, and 170 mg/kg/day for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis: Studies of valproate have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for valproate.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy: Pregnancy Category D: See WARNINGS.

Nursing Mothers: Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when divalproex sodium is administered to a nursing woman.

ADVERSE REACTIONS

Since divalproex sodium has usually been used with other antiepileptic drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to divalproex sodium alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.[3]

CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness and incoordination. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriate plasma levels; all patients recovered after the drug was withdrawn.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. A case of fatal epidermal necrolysis has been reported in a 6 month old infant taking valproate and several other concomitant medications.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation and frank hemorrhage (see PRECAUTIONS — *General* and *Drug Interactions*). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, and acute intermittent porphyria.

Hepatic: Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see WARNINGS).

Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea and parotid gland swelling. Abnormal thyroid function tests (see PRECAUTIONS).

Pancreatic: Acute pancreatitis, including fatalities.

Metabolic: Hyperammonemia (see PRECAUTIONS), hyponatremia, and inappropriate ADH secretion.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis.

Special Senses: Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established.

Other: Edema of the extremities, lupus erythematosus, and fever.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. *Fatalities have been reported.*

The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution.

DOSAGE AND ADMINISTRATION

DEPAKOTE tablets and Sprinkle capsules are administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

Administration of Sprinkle Capsule: DEPAKOTE Sprinkle capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoonful) of soft food such as applesauce or pudding. The drug/food mixture should be swallowed immediately (avoid chewing) and not stored for future use. Each capsule is oversized to allow ease of opening.

Conversion from DEPAKENE to DEPAKOTE: In patients previously receiving DEPAKENE (valproic acid) therapy, DEPAKOTE products should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on a DEPAKOTE product, a dosing schedule of two or three times a day may be elected in selected patients.[4]

DEPAKOTE products provide equal extents of absorption, although they may not produce identical trough and peak valproate concentrations. DEPAKOTE tablets produce slightly higher peak concentrations than DEPAKOTE Sprinkle capsules. Such differences in the maximum and minimum valproate plasma concentrations are unlikely to be of clinical significance; however, changes in dosage administration of valproate or concomitant medications should be accompanied by increased monitoring of plasma concentrations of valproate and other medications, as well as the patient's clinical status.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum concentration and therapeutic effect. However, therapeutic valproate serum concentrations for most patients will range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY)

As the DEPAKOTE dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected. (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

HOW SUPPLIED

DEPAKOTE Sprinkle capsules (divalproex sodium coated particles in capsules), 125 mg, are white opaque and blue, and are supplied in bottles of 100 (NDC 0074-6114-13) and Abbo-Pac® unit dose packages of 100 (NDC 0074-6114-11).

DEPAKOTE tablets (divalproex sodium delayed-release tablets) are supplied as:

125 mg salmon pink-colored tablets:	
Bottles of 100	(NDC 0074-6212-13)
Abbo-Pac® unit dose packages of 100	(NDC 0074-6212-11)
250 mg peach-colored tablets:	
Bottles of 100	(NDC 0074-6214-13)
Bottles of 500	(NDC 0074-6214-53)
Abbo-Pac® unit dose packages of 100	(NDC 0074-6214-11)
500 mg lavender-colored tablets:	
Bottles of 100	(NDC 0074-6215-13)
Bottles of 500	(NDC 0074-6215-53)
Abbo-Pac® unit dose packages of 100	(NDC 0074-6215-11)

Recommended Storage: Store tablets below 86°F (30°C).
Store capsules below 77°F (25°C).

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Revised: February, 1992

Caution — Federal (USA) Law prohibits dispensing without prescription.

Age-Related Differences in Volumes of Subcortical Nuclei, Brain Matter, and Cerebrospinal Fluid in Healthy Men as Measured With Magnetic Resonance Imaging

Declan G. M. Murphy, MD; Charles DeCarli, MD; Mark B. Schapiro, MD; Stanley I. Rapoport, MD; Barry Horwitz, PhD

• Magnetic resonance imaging was used to determine the volumes of brain, subcortical gray matter nuclei, and the ventricular and sulcal cerebrospinal fluid in 27 healthy men. Subjects were divided into young (<35 years, n=10) and old (>60 years, n= 17) groups. Volumes were normalized as percent intracranial volume. Older subjects had significantly less brain mass and significantly larger ventricular and peripheral cerebrospinal fluid volumes than the younger men. The caudate and lenticular nuclei were significantly smaller in older than younger men. This significant difference remained when their volumes were expressed as a ratio of cerebral brain matter volume. This cross-sectional study demonstrates age-related atrophy and concurrent dilation of cerebrospinal fluid spaces in healthy subjects. Of brain regions affected, the caudate and lenticular nuclei are significantly more affected by healthy aging than is cerebral brain matter; this may account for some of the motor abnormalities in aging.

(*Arch Neurol.* 1992;49:839-845)

Postmortem studies of age-related structural changes in the human brain have reported decreases in brain weight, brain volume, cerebral cortex volume, basal ganglia volume, and cell density in the cerebral cortex and basal ganglia.[1-8] However, postmortem studies have several limitations, such as fixation artifacts and patient selection bias, which in vivo imaging studies avoid. Accordingly, attempts have been made to study brain morphometrics with in vivo techniques.

This laboratory previously described[9,10] a method to quantify the volumes of gray matter, white matter, and cerebrospinal fluid (CSF) in computed tomographic (CT) images of the human brain, as well as volumes of the thalamus, lenticular nucleus, and caudate nucleus. In cross-sectional studies, aging in healthy men correlated with decreased volume of cerebral gray matter, lenticular nucleus, thalamus, and right caudate nucleus.[9,10] The volumes of CSF, right and left lateral ventricles, and third ventricle increased with age, consistent with other studies.[11-17]

Cross-sectional volumetric CT analysis of CSF spaces in normal human aging has revealed nonlinear increases beginning in the fourth decade of life.[11,17] The relation between changes in the volume of the CSF spaces and cognition with age remains unclear, because the studies have not used carefully screened healthy subjects,[14] or have used a young population with a narrow IQ range.[18] In addition, most studies have failed to partial out the effect of subject age on the correlation between cognitive function and ventricular volume. In a longitudinal CT study carried out by this laboratory, in which the effect of age was partialled out, there was no significant relation between any ventricular volume and cognitive function in healthy subjects.[17]

Computed tomographic scans are limited by their spatial resolution and tissue contrast differences, by partial voluming artifacts, and by an artifactual elevation (bone hardening) of brain CT numbers adjacent to the skull, particularly in more apical scans,[19,20] making them unreliable for measuring subarachnoid CSF. Unlike CT, magnetic resonance imaging (MRI) requires no ionizing radiation, repeated measures are without known risk, and MRI images are free of bone hardening artifacts.[21]

Magnetic resonance imaging studies have reported statistically significant age-related decreases in the volumes of cerebral cortex,[22] cerebral gray matter,[23] caudate nucleus,[23,24] putamen,[25] and anterior diencephalic gray matter structures (defined as septal nuclei, anterior hypothalamic gray matter, and some basal forebrain regions).[23] Cerebral white matter of the elderly has been reported to display both lengthened T_2 values[23] and more cortical and subcortical leukoariosis.[26-30] Ventricular and sulcal CSF volumes correlate positively with age.[22] However, not all of these MRI studies have established evidence of good health in all subjects. Only one controlled for head size,[23] and none compared age-related atrophy of subcortical nuclei with atrophy of the cerebral hemispheres.

We therefore decided to perform a quantitative morphometric MRI study of the brain in relation to healthy aging. Our study differs from others[22-25] because (1) we examined the effect of age in one sex only, so no confounding gender effects are present, (2) we controlled for the potential secular effect of aging on head size, and (3) we compared age-related changes in volumes of the subcortical nuclei with volume changes of the cerebral hemispheres.

Computerized approaches were employed to measure the volumes of subcortical gray matter nuclei, cerebral ventricles, cerebral brain matter, and ventricular and peripheral CSF. The subjects were free of primary brain disease or of conditions that might contribute to brain disease. To our knowledge, this is the first MRI study (1) to show significant age-related atrophy in the lenticular nuclei after controlling

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Reprint requests to Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892 (Dr Murphy).

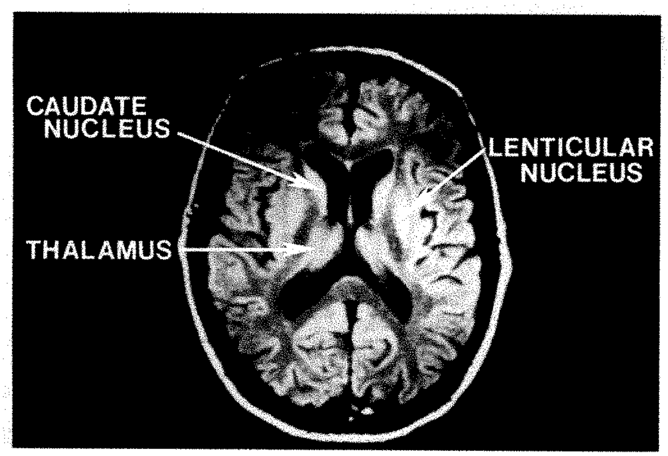

Fig 1.—*Method of magnetic resonance imaging analysis for axial images. Equalized magnetic resonance imaging scans were used to measure volumes of the subcortical nuclei as noted.*

for subject intracranial volume and (2) to find that the aging process is more correlated with the volumes of the caudate and lenticular nuclei than of the cerebral hemispheres. An abstract of this work has been presented.[31]

SUBJECTS AND METHODS

Subjects

Twenty-seven healthy male volunteers between the ages of 19 and 92 years were screened medically, neurologically, and by laboratory tests to exclude primary brain disease and conditions that contribute to brain disease, such as hypertension, cardiovascular disease, head trauma, atherosclerosis, diabetes, drug abuse, alcohol abuse, or a major psychiatric disorder.[32] The subjects were divided into young (<35 years) and old groups (>60 years) for analysis. Ten were in the young group (mean [±SD] age, 25±4 years; range, 19 to 33 years), and 17 were in the old group (73±7 years; range, 64 to 92 years). Subjects were participants in a clinical program on brain aging conducted by the Laboratory of Neuroscience of the National Institute on Aging, Bethesda, Md. No subject had a focal cerebral abnormality detected by CT scan. All were free of extrapyramidal symptoms after being screened by clinical history and a structured neurological examination.[33] No subject had a memory disorder as measured by clinical history, the Mini-Mental State examination,[34] or the Blessed Memory, Information, and Concentration Test.[35]

MRI Scanning

Magnetic resonance imaging of the brain was performed on a 0.5-Tesla scanner (Picker Instruments, Cleveland, Ohio). Axial slices were analyzed, using the proton density (repetition time, 2000 milliseconds; echo time, 20 milliseconds) portion of a double echo sequence (repetition time, 2000/20/80 milliseconds) with 192 views and two repetitions. Thirty-six contiguous slices, 7 mm thick, were obtained from the foramen magnum to the vertex, parallel to the inferior orbitomeatal line. Image acquisition time for the double echo sequence was 25 minutes. Data, stored on magnetic tape in digital form, were analyzed with a VAX 11/750 computer system (Digital Equipment Corp, Landover, Md) and a Gould 8400 Image Array Processor (Vicom Inc, Fairfax, Va) after being displayed on a television monitor. Subjects' scans were analyzed by operators after being loaded in random order by a research assistant; operators were "blind" to subject name, age, and group.

Methods of Analysis

A region of interest (ROI) analysis was applied to determine the volumes of the cerebral ventricles, cerebral hemispheres, and subcortical nuclei. Subcortical nuclei were traced after employing a histogram equalization method to enhance the contrast between gray and white matter (Vicom Inc, Lips Version 4.1, October 1985, Fairfax) (Fig 1). The cerebral ventricles and hemispheres were traced on unequalized images, and a segmentation analysis (Fig 2) was used on the unequalized image to determine volumes of total CSF space and of cerebral brain matter (defined as cerebral white plus gray matter). Peripheral CSF volume was calculated by subtracting ventricular CSF volume from the total CSF volume determined by segmentation. Asymmetries were estimated for the volumes of the subcortical nuclei, CSF, and cerebral brain matter. Absolute volumes (in cubic centimeters) were calculated, as well as volumes as a percent of the traced intracranial volume, to control for the relation of head size to volumes of cerebral structures.[10] Intracranial volume was defined as cerebral hemispheres plus brain stem and cerebellum.

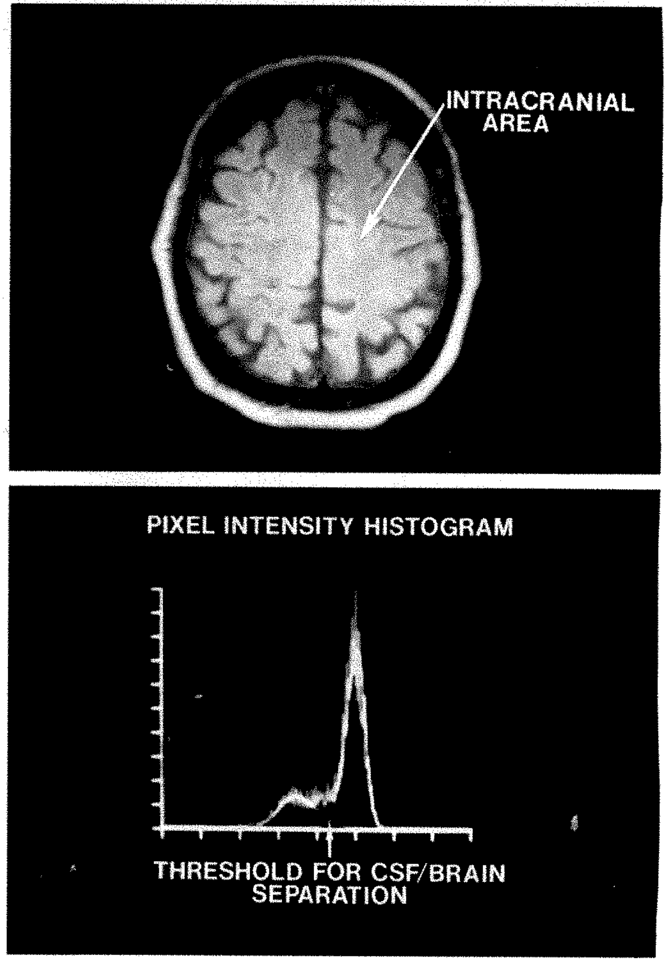

Fig 2.—*Method of magnetic resonance imaging analysis for axial images. Pixel intensity histogram of a magnetic resonance image, demonstrating the threshold for cerebrospinal fluid and brain matter as noted.*

Regions of Interest.—In a given MRI scan, the operator traced the total cerebral hemispheric cross-sectional area (square centimeters) and outlined the right and left hemispheres (brain matter plus CSF), lateral and third ventricles, cerebellum, and brain stem. The medial surfaces of the cerebral hemispheres were bisected by following the dura into the interhemispheric fissure and then drawing a straight line connecting the anterior to the posterior interhemispheric fissure.

Regions of interest were traced on each axial image in which they were present. The subcortical nuclei were traced after employing a histogram equalization method to enhance the contrast between gray and white matter (Fig 1). After equalization, the following ROIs were traced if present: right and left caudate nuclei, right and left lenticular nuclei, and right and left thalamus.

The number of enclosed pixels ($1\ \text{pixel}=1\ \text{mm}^2$) was determined for each ROI on every slice in which it was present. The volume of each ROI (in cubic centimeters) was calculated by multiplying the summed pixel cross-sectional areas by slice thickness (7 mm).

Segmentation Analysis.—To quantify CSF and brain matter in each slice, we used a previously published semiautomated method based on mathematical modeling of MRI pixel intensity histograms.[36] On each axial image, the operator first outlined the intracranial area and then used nonlinear modeling of the pixel intensity histogram to find an optimal threshold for separating CSF from brain matter pixels (Fig 2). The operator then returned to the image and outlined each cerebral hemisphere for segmentation of CSF from brain matter, using the global threshold value just obtained. With this method, the volumes of the following structures were calculated: total hemispheric brain matter, total CSF, right hemisphere brain matter, left hemisphere brain matter, right hemisphere CSF, and left hemisphere CSF.

Derived Values.—The volume of peripheral CSF was calculated by subtracting the sum of the traced ventricular CSF volumes from the total cerebral CSF volume obtained by segmentation (eg, Right Peripheral CSF Volume=Right Hemisphere CSF Volume−Right Lateral Ventricle Volume−[Third Ventricle Volume/2]). Left-right asymmetries were calculated for gray matter nuclei, cerebral brain matter, and CSF by subtracting the right-sided volume from the left-sided volume and dividing by the total intracranial volume. For example, lateral cerebral ventricular volume asymmetry was calculated as follows: (Volume Left Lateral Ventricle−Volume Right Lateral Ventricle)/Total Intracranial Volume.

Traced volumes of each ROI were expressed as a percent of the traced intracranial volume to control for head size (Table 1). In addition, the total volumes (right plus left) of the caudate, lenticular, and thalamic nuclei were divided by the total cerebral brain matter volume to determine if disproportionate atrophy occurred in the subcortical nuclei as compared with cerebral hemispheric brain matter using the following formula: Nonnormalized Subcortical Nucleus Volume/(Total Cerebral Brain Matter Volume−Nonnormalized Subcortical Nucleus Volume). Cerebral brain matter volume was defined as brain matter volume of the cerebral hemispheres.

Reliability

Intrarater and interrater reliabilities were determined for all brain ROIs traced by the operators as part of this analysis. Highly significant interrater and intrarater reliabilities were obtained for all ROIs. The interrater correlation coefficient was $F>4.0$ and $P<.01$ in all cases.[36]

Statistics

All comparisons of means between the old and the young groups used unpaired Student's t tests; an F test was used to assess within-group variance. Within-group asymmetry of ROI volumes was determined using paired t tests. Statistical significance was defined as $P<.05$ for all analyses.[37] All values are given as mean±SD. Statistical comparisons were carried out only on normalized volumes because, given that brain weight is related to body height, and given that body height has increased over the last century, younger subjects' brains may be larger than older subjects' solely from this secular effect.[38-40]

RESULTS

As illustrated in Table 2, mean pulse rate and mean systolic and diastolic blood pressure were not significantly different between old and young men ($P>.05$). The older group was more educated (18±1.5 years) than the young (16±2 years) and had significantly higher Wechsler Adult Intelligence Scale (WAIS) Full-Scale, Verbal, and Performance IQs[41] (age corrected) than the young subjects but had a significantly lower WAIS Performance scaled score. Scaled scores are not age corrected. No significant difference was found between the two groups for the WAIS Verbal scaled score. A significant age-related decline in WAIS Performance scaled scores has been reported.[10,32,41-43]

Absolute volumes (in cubic centimeters) of all measured ROIs in the young and old subjects are presented in Table 3.[8, 44-49] They are consistent with autopsy-derived volumes of cerebral structures.[8,44-47] The ROI volumes and derived values, corrected for intracranial volume, are presented in Table 1. Statistical comparisons for all ROIs and derived values were carried out only on values normalized to intracranial volume.

Table 1.—Volume of Intracranial Structures and CSF in Young and Old Healthy Men as Measured by MRI*

Structure	Young Men	Old Men
Hemisphere		
R	43.5±1.3	44.2±1.6
L	43.9±1.1	44.5±1.8
Hemispheric brain matter		
Total	80.7±2.7	75.9±3.7†
R	39.9±1.4	38.4±2.2
L	39.9±1.4	38.4±2.0†
Subcortical nuclei		
Thalamus		
R	0.55±0.08	0.50±0.09
L	0.57±0.09	0.53±0.06
Lenticular nucleus		
R	0.57±0.11	0.47±0.13†
L	0.65±0.10	0.44±0.14†
Caudate nucleus		
R	0.45±0.09	0.35±0.09†
L	0.47±0.09	0.37±0.09†
Total and peripheral CSF		
Hemisphere		
Total	7.72±2.67	12.2±3.33†
R	3.57±1.25	5.84±1.65†
L	4.03±1.40	6.42±1.70†
Peripheral CSF		
Total	6.79±2.45	10.6±2.71†
R	3.12±1.13	5.03±1.35†
L	3.56±1.29	5.57±1.38†
Ventricular CSF		
Lateral ventricle		
R	0.41±0.20	0.77±0.50†
L	0.44±0.20	0.79±0.48†
Third ventricle	0.06±0.03	0.09±0.04†
L-R asymmetry $(\times 10^{-2})$, %		
CSF		
Ventricular	3.30±1.40	2.60±1.39
Peripheral	43.7±38.3‡	54.6±57.2‡
Nuclei		
Caudate	2.35±3.90	2.01±6.60
Thalamic	2.17±4.05	2.80±8.56
Lenticular	7.73±9.29	−3.79±5.68†
Brain matter	−1.98±4.07	−1.53±10.4

*CSF indicates cerebrospinal fluid; MRI, magnetic resonance imaging. Values are cubic centimeters, mean±SD, expressed as a percentage of intracranial volume: 100×(Structure Volume/Total Cranial Volume). Left-Right Asymmetry=(Volume of Left-Sided Structure−Volume of Right-Sided Structure)/Intracranial Volume. Cerebral Hemisphere Volume=Brain Matter+CSF.

†Old significantly different than young by Student's t test, $P<.05$.

‡Significant left-right differences within group by paired t test, $P<.05$.

The older men had significantly less total cerebral hemispheric brain matter, as well as left hemisphere brain matter, than did the younger men. The older men also had significantly larger volumes in every CSF measure (Table 1, Fig 3). There were no significant left-right differences in ventricular CSF or brain matter volumes; however, both the old and young men had significantly more left- than right-sided peripheral CSF.

Table 2.—Characteristics of Subjects*

Variable	Young Men (n=10)	Old Men (n=17)
Age, y	25±4	73±8
Heart rate, beats per min	71±12	68±11
Blood pressure, mm Hg		
Systolic	119±13	121±12
Diastolic	74±6	76±8
Education, y	16±2	18±1.5†
WAIS Full-Scale IQ	122±11	133±7†
WAIS Verbal IQ	126±9	136±9†
WAIS Performance IQ	114±13	124±8†
WAIS Performance scaled score	60±10	47±9†
WAIS Verbal scaled score	86±9	86±10

*All values are mean±SD. WAIS indicates Wechsler Adult Intelligence Scale.

†Mean of old men significantly different than mean of young men ($P<.05$), Student's *t* test.

Normalized volumes of the lenticular and caudate nuclei were significantly smaller in the old than young men. This also was true when volumes of the subcortical nuclei were expressed as a percent of brain matter volume (Table 4, Fig 4). Thus, volumes of the caudate and lenticular nuclei were reduced more in the old than was the volume of cerebral brain matter. The right lenticular nucleus was significantly larger than the left in the older men, whereas in the young men the reverse was true. However, volumes of the thalamic nuclei did not differ significantly between the old and the young groups. There was no significant asymmetry in the volumes of the caudate or thalamic nuclei in either the old or the young men.

COMMENT

This cross-sectional MRI study quantifies brain matter atrophy, subcortical gray matter atrophy, ventricular dilatation, and expansion of peripheral CSF volume in 10 young (mean, 25±4 years; range, 19 to 33 years) and 17 old (mean, 73±7 years; range, 64 to 92 years) healthy men. All subjects were free of evidence of brain disease and of conditions that might contribute to subclinical brain disease. The absence of a significant age difference in systolic blood pressure attests to the excellent health of our subjects, because blood pressure rises with age in the general population.[50] Not all CT or MRI studies of aging have established such evidence of good health in all subjects.[14,23]

Our MRI-derived absolute volumes allow comparison with other MRI and CT studies as well as with the neuroanatomical literature (Table 3). The absolute volumes of cerebral structures and CSF closely agree with neuroanatomical findings (Table 3), and they are more consistent with them than are values derived by CT.[10] For example, autopsy studies of young men show a mean total CSF space of 110 cm^3 and a caudate nucleus volume of 4.6 to 8.6 cm.[38,44-47] Using MRI, we obtained volumes of 115±50 cm^3 and 6.5±0.5 cm^3, respectively. In contrast, the volumes of the same structures measured by quantitative CT[10] were 18.9±9.1 cm^3 and 2.6±0.78 cm^3. In addition, we normalized our data by dividing the volume of the structures by total intracranial volume. This correction was performed because, given that brain weight is related to body height, and that body height has increased over the last century, younger subjects' brains may be larger than older subjects' solely from this secular effect.[38-40]

In our previous CT study[10] of healthy adult men, age was correlated with increased volumes of CSF, the lateral ventricles, and the third ventricle. However, peripheral CSF was grossly underestimated because of the bone hardening artifact. Age also was correlated with decreased volumes of cerebral gray matter and of individual subcortical nuclei.

The volumes of structures in this MRI study are in closer agreement with the neuroanatomical literature (Table 3) than are volumes obtained previously with CT.[10] The latter analysis[10] used slices that were 10 mm thick and were separated from adjacent slices by 7 mm, introducing substantial error. In contrast, our MRI analysis used 7-mm-thick slices that were contiguous. Other reasons for more accurate MRI data include the superior tissue contrast and spatial resolution, fewer partial voluming artifacts, and the difficulty of measuring nonventricular CSF with CT due to the artifactual elevation of brain CT numbers adjacent to the skull.[19,20]

Other CT studies[11-18] have shown a consistent asymmetry of the lateral ventricles in humans, with the left lateral ventricle being bigger than the right in over 95% of subjects. This MRI study did not find a statistical difference between volumes of left and right lateral ventricles in old or young men. However, both groups had significantly more peripheral CSF on the left than on the right side. Cross-sectional CT studies also have found a nonlinear increase of CSF volume in relation to age and an increase in the variability of the CSF volume with age.[11-16] We found an increased variance of lateral ventricular volumes with age, but no significant increased variance of the volumes of the third ventricle or of peripheral CSF.

Prior MRI studies of aging have reported significant volume differences of the cerebral cortex,[22] cerebral gray matter,[23] subcortical gray matter structures,[23-25] cerebral ventricular and sulcal CSF,[22] and differences in the amount of cortical and subcortical leukoariosis.[26-30] However, some of these studies did not control for head size and did not compare the atrophy in these structures with the rest of the brain. Our study examined the relation of age in one sex only, thereby eliminating any confounding gender effect. Takeda and Matsuzawa[51] showed that women have smaller CSF spaces than men at each decade of life except the eighth, even after correcting for smaller head size.

The older men had significantly smaller caudate and lenticular nuclei than did the young men. This difference was present after normalizing these volumes to hemispheric brain matter volume, suggesting that the caudate and lenticular nuclei are more affected by aging than are the hemispheric structures (Table 4, Fig 4). In the older men, the right lenticular nucleus was significantly larger than the left, whereas in the young men the opposite was true. Jernigan et al[22,23] showed a decrease in the volume of the caudate but not of the lenticular nucleus with age, but we demonstrated a significant age effect in both nuclei. This discrepancy may be due to differences in technique. We used a proton density image acquisition protocol on a 0.5-Tesla machine that is not affected by iron deposition in the globus pallidus, and we left no interslice gap, whereas Jernigan et al[22,23] used relatively T_2-weighted images and left a 2.5-mm gap between successive slices. The globus pallidus may have iron deposits, which reduce signal values on T_2-weighted images,[52] and interslice gaps reduce measurement sensitivity—particularly of small, irregularly shaped structures. Our finding of a significant age difference in the volume of the

Table 3.—Volume of Intracranial Structures and CSF in Young and Old Healthy Men as Measured by MRI, Compared with Neuroanatomical Volumes*

	MRI Volumes		
Volume	Young Men	Old Men	Neuroanatomical Volumes (Age, y)[8,44-49]
Total intracranial	1477±193	1404±161.7	1500 (20)
Total cerebral	1308±185	1243±153	1200 (20)
Hemisphere			
R	643±94	620±64	. . .
L	650±95	623±63	. . .
Brain stem plus cerebellum	170±19	161±32	. . .
Hemispheric brain matter			
Total	1192±160	1067±136	. . .
R	590±81	538±59	. . .
L	590±81	538±62	. . .
Subcortical nuclei Thalamus			
R	8.0±1.4	6.9±1.0	17.2 (total thalamus volume, 55)
L	8.3±1.2	7.3±0.7	17.2 (total thalamus volume, 55)
Lenticular nucleus			
R	8.4±1.8	6.6±1.7	7.3-9.6 (20-55)
L	9.5±1.3	6.0±2.0	7.3-9.6 (20-55)
Caudate nucleus			
R	6.5±0.8	4.9±1.1	4.6-8.6 (20-55)
L	6.9±1.2	5.2±1.1	4.6-8.2 (20-55)
Total and peripheral CSF			
Hemisphere Total	116±51	172±51	110 (15-25)
R	53±23	82±25	. . .
L	60±27	90±25	. . .
Peripheral CSF			
Total	102±47	148±41	. . .
R	47±21	71±20	. . .
L	53±24	78±20	. . .
Ventricular CSF			
Lateral ventricle			
R	6.1±3.0	10.8±7.6	4.3-12.2 (20-90)
L	6.6±3.5	11.1±7.3	4.8-13.5 (20-90)
Third ventricle	0.9±0.5	1.3±0.5	0.8-1.0 (29-73)

*CSF indicates cerebrospinal fluid; MRI, magnetic resonance imaging. Values are cubic centimeters, mean±SD. Cerebral hemisphere volume=brain matter+CSF.

caudate nuclei agrees with that of Krishnan et al,[24] who used a stereological technique to measure the volume of the caudate nuclei in men and women. Our total caudate nuclei volumes of 13.4 cm^3 in young males and of 9.6 cm^3 in old males correspond well with the values found by Krishnan et al[24] of 13.3 cm^3 and 7.0 cm^3.

Relatively greater atrophy of basal ganglia nuclei with age may be related to disrupted motor function and balance in the elderly.[53] Different populations of striatal neurons show different patterns of loss with advancing age.[54] With aging there is slowing of voluntary movements and the emergence of involuntary movements similar to, but less severe than, that seen in diseases of the basal ganglia.[55-60] Indeed, age-related atrophy may contribute to the emergence of Parkinson's disease[61] and Huntington's chorea,[62] both disorders of extrapyramidal function.

A postmortem study[63] has reported that both gray and white matter atrophy occur in relation to age. The gray-white matter ratio changes during adult life, falling from 1.28 at age 20 years to a low of 1.13 at 50 years, then rising to 1.55 at 100 years. It is possible that our finding of relatively greater atrophy of basal ganglia nuclei may be due to age-related differences in the gray-white matter ratio, because our measure of the cerebral brain matter includes both gray and white matter but our subcortical measure includes only gray matter. Therefore, loss of equal proportions of cortical and subcortical gray matter volume would be masked by the relative preservation of cortical white matter, and it would appear that subcortical regions had lost proportionately more volume than cortical gray matter. However, this is unlikely, as (1) we found that the thalamus is not more affected by aging than the hemispheric structures, and (2) at the mean age of our healthy young and old men (25 and 73 years), the gray-white matter ratios are identical.[63]

Postmortem studies have reported age-related decreases in the volumes of the lenticular and the caudate nuclei,[8] and in neuronal density of the putamen.[7] Other brain areas, such as the abducens nucleus, show no cell loss with aging.[64] In addition, there are age-related differences in brain neurochemistry, especially in the dopaminergic neurons of the nigrostriatal tract. Concentrations of tyrosine hydroxylase decrease nonlinearly with age in the human caudate, putamen, and nucleus accumbens.[65] Dopamine levels decline linearly with age in the caudate nucleus.[66]

Positron emission tomographic studies of in vivo D_2 dopamine receptor binding have shown a linear decrease in striatal D_2 dopamine receptor binding with age.[67,68] The nigrostriatal dopaminergic neurons have been studied using positron emission tomography and L-6[^{18}F] fluoro-Dopa

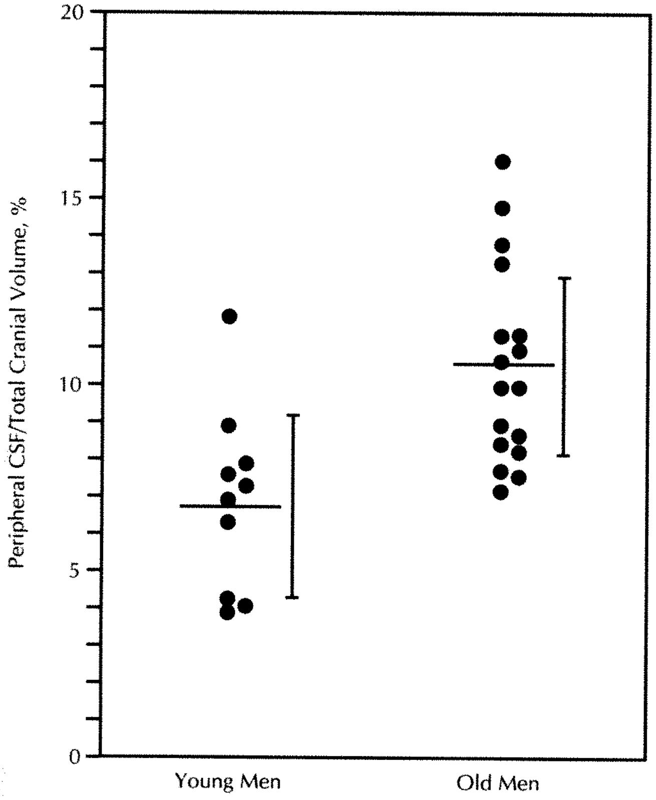

Fig 3.—*Peripheral cerebrospinal fluid volume as a percent of total cranial volume of healthy young and old men. Solid horizontal bar represents the population mean; solid vertical bar, the population SD.*

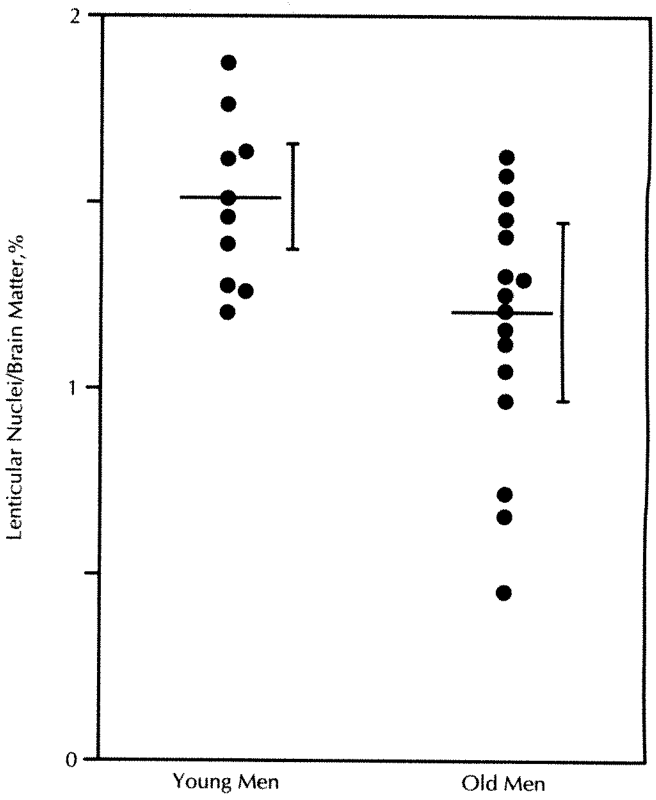

Fig 4.—*Lenticular nuclei volumes as a percent of cerebral hemispheric brain matter volume of healthy young and old men. Volumes on the y-axis are are total lenticular nuclei volumes/total cerebral hemispheric brain matter, percent. Solid horizontal bar represents the population mean; solid vertical bar, the population SD.*

Table 4.—Volumes of Subcortical Nuclei as Percent of Brain Matter Volume*

Nucleus Structure	Young Men	Old Men
Caudate	11.59±2.41	9.64±2.19†
Thalamic	14.06±2.39	13.69±1.55
Lenticular	15.41±2.33	12.05±3.37†

*All values are 100×(Structure volume/cerebral brain matter volume), mean±SD, cubic centimeters.

†Old significantly different than young ($P<.05$) by two-tailed Student's *t* test.

(^{18}F-Dopa). One such study[69] reported an age-related decline in total striatal ^{18}F-Dopa uptake, whereas another found no difference.[70] Positron emission tomographic studies with ^{18}F 2-deoxy-D-glucose have demonstrated that cerebral metabolic rates for glucose in the caudate and the lenticular nuclei are not correlated significantly with age.[71,72] The absence of an age effect may be because metabolic rates are per gram of tissue and not for an entire structure. Other explanations include heterogeneity of brain structure and metabolism and redundancy and plasticity of the human brain.

None of our subjects had extrapyramidal signs. However, it could be that a critical threshold of tissue loss has to be reached before symptoms occur. This may explain why the size of the subcortical nuclei could be significantly reduced in our population without accompanying symptoms.

In summary, this study quantifies brain atrophy, subcortical gray matter atrophy, ventricular dilatation, and expansion of peripheral CSF in 10 young and 17 old healthy men. This is the first MRI study (1) to show significantage-related atrophy in the lenticular nuclei after having controlled for head size, and (2) to find that the healthy aging process affects the caudate and the lenticular nuclei significantly more than the cerebral hemispheres. Such atrophy may, when reaching a critical threshold, contribute to some of the motor abnormalities that accompany aging.

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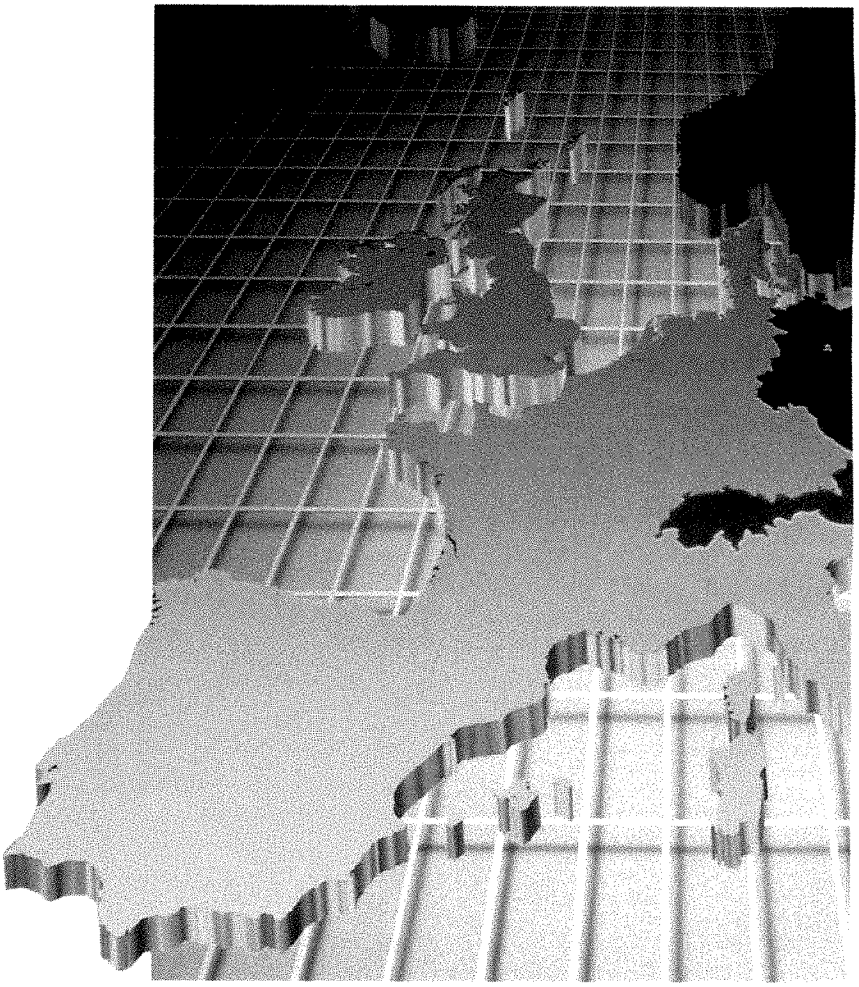

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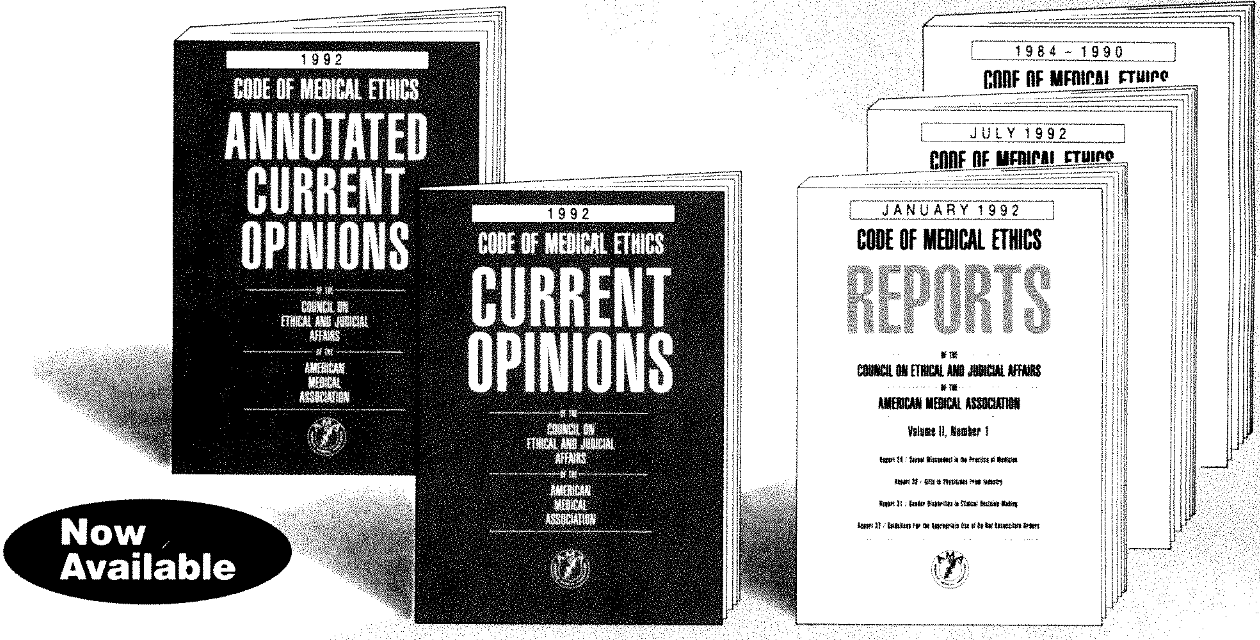
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Cerebral Glucose Utilization in Motor Neuron Disease

John M. Hoffman, MD; John C. Mazziotta, MD, PhD; Thomas C. Hawk; Ron Sumida

• Positron emission tomography with fludeoxyglucose F 18 (^{18}F-fluorodeoxyglucose) was used to examine regional cerebral glucose metabolism in individuals with motor neuron disease. Motor neuron disease involves selective loss of motor neurons, large pyramidal cells in the motor cortex, and corticospinal tract degeneration. We postulated that the local cerebral metabolic rate of glucose should correlate with this regional neuronal cell loss. Glucose metabolism values in patients with motor neuron disease were reduced compared with those of controls in several regions; however, when corrected for multiple comparisons, no significant difference was observed between patients with motor neuron disease and age-matched controls. No correlation was noted between the local cerebral metabolic rate of glucose and duration or severity of illness. Correlation between metabolic changes with objective findings on neurologic examination, including motor weakness and tendon reflexes, provided interesting results, including a decline in glucose metabolism with progressive weakness and upper motor neuron dysfunction. Moreover, in supplementary motor areas, there appears to be an increase in regional glucose metabolism as the neurologic condition deteriorates, possibly representing increased metabolic activity of the motor association cortex in response to primary loss of pyramidal cells.

(*Arch Neurol.* 1992;49:849-854)

Motor neuron disease (MND) is a heterogeneous group of progressive degenerative diseases clinically affecting the voluntary motor system. Pathologically, the cerebral cortex, pyramidal structures, brain stem, anterior horn cells, and spinal cord can be involved.[1-3] Amyotrophic lateral sclerosis (ALS), a specific form of MND, effects, to varying degrees, spinal and bulbar lower motor neurons (LMNs) and upper motor neurons (UMNs.)[4] The worldwide incidence is approximately 0.4 to 1.8 per 100 000, with a 1 to 1.6:1 male-to-female ratio.[5] Median age at onset is 55 years, with death typically occurring 3 to 5 years later. Bulbar involvement is associated with a more rapid decline.[5-9] Individuals with purely spinal LMN involvement (progressive muscular atrophy) often have a less rapid clinical deterioration. Symptoms of ALS can include weakness, cramping, and observable muscle twitching or fasiculation. With bulbar involvement, dysarthria and dysphagia are prominent problems. Death typically occurs from pulmonary complications. Clinical signs include atrophy, spasticity, fasiculations, weakness, reflex changes, evidence of corticospinal tract dysfunction, and intact sensory function.[2]

Despite extensive epidemiologic and scientific investigations, no cause of MND has been identified.[10] The differential diagnosis of syndromes causing similar clinical findings includes toxin exposure (eg, mercury,[11] lead, or tricreosyl phosphate poisoning), remote effects of neoplasia,[12] hypoglycemia,[13,14] and cervical spondylosis. In their recently published excellent review, Mitsumoto et al[5] discuss historical, clinical, epidemiologic, biochemical, metabolic, and immunologic theories concerning the cause of MND. With a complete neurologic examination, appropriate laboratory studies, and confirmation of denervation changes (ie, electromyography and/or biopsy), indicating widespread anterior horn cell disease, the diagnosis can be made with confidence. Various therapies have been proposed; however, none has proved to be efficacious.[15-19]

Herein, we correlate known neuropathologic changes observed in MND with the local cerebral metabolic rate for glucose (LCMRGlc) using fludeoxyglucose F 18 (^{18}F-fluorodeoxyglucose) (FDG) and positron emission tomography (PET). Because LCMRGlc reflects neuronal synaptic metabolic activity in healthy adults[20,21] and because MND involves selective loss of motor neurons, large pyramidal cells in motor cortex, and corticospinal tract degeneration,[1,2,22] we hypothesized that reduced LCMRGlc should parallel this regional neuronal cell loss.

PATIENTS, SUBJECTS, AND METHODS

Patients and Subjects

We performed 10 FDG-PET studies in seven patients (six male and one female) aged 37 to 70 years (mean[±SD], 57.3±12.8 years). Three men underwent a repeated study approximately 1 year after the initial FDG-PET examination. Six of the seven subjects had classic ALS with both UMN and LMN involvement. One subject had strictly LMN findings, and three subjects had associated bulbar involvement (Table 1).

All subjects were otherwise healthy and without other substantial medical illnesses. The patients with MND all underwent thorough neurologic examinations. Standard grading of motor strength,[23] tendon reflexes, and corticospinal tract function was used. Patients had electromyographic evidence of MND, a normal myelogram, and/or a spinal magnetic resonance imaging scan, and were diagnosed independently by two neurologists. In four of the seven subjects, computed tomographic or magnetic resonance imaging brain scans were normal. None of the subjects were receiving medication at the time of the FDG-PET study. Patients with MND were compared with an age-matched control population of 11 neurologically normal subjects aged 37 to 69 years (mean [±SD], 56.7±11.85 years; six male and five female). None of the patients with MND showed evidence of respiratory compromise or nutritional abnormalities, such as dehydration or ketosis at the time of the FDG-PET study.

PET Studies

Subjects were placed in the recumbent position with their eyes and ears open in a room with dim fluorescent indirect lighting and

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Reprint requests to the Division of Nuclear Medicine, Box 3949, Duke University Medical Center, Durham, NC 27710 (Dr Hoffman).

Table 1.—Neurologic Status in Subjects With Motor Neuron Disease*

Study No./Age, y/Sex	Upper Motor Neuron Involvement	Bulbar (Cranial Nerve) Involvement	Severity†	Duration of Motor Neuron Disease, y
1/64/M	Yes	No	3	5
2/65/M	Yes	No	5	6
3/40/M	Yes	No	2	5
4/41/M	Yes	No	3	6
5/69/M	Yes	No	4	5
6/70/M	Yes	No	5	6
7/37/M	Yes	Yes	5	5
8/66/F	No	No	2	3
9/62/M	Yes	Yes	3	2
10/59/M	Yes	Yes	7	1

*Three of the seven total patients were studied twice. All patients had a normal nutritional status; in several patients, disease progressed slowly.
†See text for explanation of severity rating scale.

background fan noise from the tomograph. During the 40-minute FDG uptake period, the subjects remained quiet, and verbal interactions were avoided. All intravenous lines were placed 10 to 15 minutes before the injection of the tracer. "Arterialized" venous blood sampling was used to obtain the FDG plasma input function.[24] All subjects were studied in accordance with the policies of the UCLA Human Subject Protection Committee.

Fluorine-18 was produced in the UCLA cyclotron, and FDG was synthesized by a semiautomated method.[25] The injected intravenous dose of FDG was 222 to 370 MBq. Scans were obtained with the NeuroECAT tomograph (CTI, Knoxville, Tenn). The full width at half-maximum image resolution was 9.5 mm in the image plane and 12.4 mm in the axial plane. Two to three million counts per image plane were obtained.[26] Attenuation correction was performed with use of the geometric method, as has been previously described.[27,28] A total of 12 cross-sectional tomographic planes were obtained parallel to the canthomeatal line with 8-mm center-to-center spacing.

Metabolic rates for glucose were determined for specific neuroanatomic regions, as previously described.[24,29,30] The LCMRGlc of regions of interest (ROIs) for subcortical, cortical, and white-matter zones known to be part of the motor system were determined.[30] Structures that spanned more than one tomographic plane (eg, thalamus and caudate nucleus) were assigned three-dimensional values for LCMRGlc by the following scheme. Both the average planar metabolic rate and cross-sectional area of the region in each tomographic plane were determined. The three-dimensional metabolic rate for glucose was weighted by the cross-sectional area of a given plane according to the following equation:

$$MR_w=\sum_{i=1}^{N}(MR)_i(A)_i/A_i\sum_{i=1}^{N}$$

where MR_w indicates three-dimensional weighted (by area) metabolic rate for a structure; MR_i, the planar metabolic rate value of a structure in plane i; and A_i, the cross-sectional area of the structure in plane i (N is the number of planes that include the structure). With this technique, weighted three-dimensional LCMRGlc values were obtained for all neuroanatomic structures of interest. Weighted normalized values were obtained by dividing the weighted LCMRGlc of each neuroanatomic structure by the ipsilateral cerebral hemispheric weighted LCMRGlc. Weighted normalized values were determined for 17 different bilateral ROIs (Table 2).

Statistical Analysis

It was hypothesized that the severity of MND symptoms would correlate with progressive neuronal degeneration and inversely with the LCMRGlc. To test this hypothesis, a severity rating scale was devised, in which 0 indicated normal; 1, neurologic signs in one or two extremities; 2, "more pronounced" signs than observed in 1; 3, same as 2 plus bulbar involvement or all extremities involved; 4, more pronounced than 3 and difficulty with ambulation; 5, requires assistance with transfers; 6, nonambulatory; 7, nonambulatory with bulbar and/or respiratory involvement; 8, bedridden with profound loss of motor function; 9, ventilator dependent with minimal motor function; and 10, ventilator dependent with no motor function. In this study, severity ratings ranged from 2 to 7. In patients studied on two occasions, disease progressed during the 1-year follow-up period. A Spearman Rank-Order Correlation analysis was used to determine the effects of severity of disease as well as duration of disease on the LCMRGlc for the 17 ROIs. Other statistical studies performed included a two-tailed Student *t* test with Bonferroni correction to compare the mean regional LCMRGlc in patients with MND with that of the control population. Analysis of variance was used to examine possible relationships between LCMRGlc and objective neurologic signs, such as motor strength and tendon reflexes. For the purposes of this analysis, each extremity was given a motor strength value corresponding to the weakest muscle group in that extremity. Likewise, the tendon reflex value corresponding to the most pathologic reflex noted in the entire extremity was used. It should be noted that even though the most pathologic muscle group or reflex was used to grade the entire extremity in our subjects, each extremity was fairly uniform in its involvement (ie, motor strength and deep tendon reflexes).

As previously noted (Table 1), all but one subject had evidence of UMN involvement, which was defined as increased reflexes, extensor plantar responses, or increased tone.

RESULTS

Typical FDG-PET images from studies numbered 1 and 10 (from Table 1) are shown in Fig 1. Weighted normalized cerebral metabolic rates of glucose for the patients with MND and controls are shown in Table 2. Values for the total number of studies (n=10) rather than individuals (n=7) are shown. The LCMRGlc values in patients with MND were different from those in controls for the frontal white matter, right superior cerebellum, right precentral gyrus, left middle temporal gyrus, head of caudate, and dentate of the cerebellum. Following a Bonferroni correction for multiple comparisons (P=.05/17 ROIs=.003), however, there were no significant differences between weighted normalized LCMRGlc values in patients with MND and age-matched controls.

Analyses performed to correlate metabolic changes with objective findings on neurologic examination are summarized in Fig 2. The precentral gyrus and middle frontal gy-

Table 2.—Cerebral Metabolic Rate of Glucose*

Brain Region	MND Left	Control Left	MND Right	Control Right
Precentral gyrus	1.02±0.05	1.03±0.03	0.96±0.05	1.01±0.04
Lateral superior frontal gyrus	0.98±0.10	1.01±0.08	0.95±0.11	0.99±0.09
Medial superior frontal gyrus	1.15±0.13	1.06±0.14	1.11±0.14	1.08±0.14
Middle frontal gyrus	1.12±0.08	1.07±0.07	1.10±0.08	1.07±0.05
Inferior frontal gyrus	1.11±0.08	1.06±0.03	1.03±0.07	1.00±0.05
Superior parietal lobule	0.97±0.10	0.94±0.11	0.95±0.09	0.95±0.09
Inferior parietal lobule	1.04±0.05	1.04±0.07	1.02±0.06	1.02±0.05
Middle temporal gyrus	1.02±0.07	0.92±0.05	1.00±0.11	0.92±0.05
Head of caudate	1.20±0.05	1.29±0.05	1.25±0.06	1.33±0.04
Body of caudate	1.22±0.08	1.20±0.14	1.20±0.10	1.21±0.10
Thalamus	1.23±0.09	1.28±0.06	1.26±0.09	1.30±0.06
Vermis-cerebellum	. . .	. . .	0.85±0.13	0.97±0.04
Dentate-cerebellum	0.81±0.09	0.93±0.04	0.81±0.11	0.94±0.04
Superior lobule cerebellum	0.72±0.09	0.80±0.3	0.70±0.9	0.81±0.05
Midbrain	. . .	. . .	0.95±0.08	0.93±0.07
Pons	. . .	. . .	0.71±0.09	0.78±0.04
Frontal white matter	0.77±0.03	0.70±0.65	0.80±0.04	0.72±0.03

*Values (mean±1 SD) are weighted normalized (see text for explanation). MND indicates motor neuron disease. A significant ($P<.05$) reduction in local cerebral metabolic rate of glucose (LCMRGlc) when compared with controls was noted for the right precentral gyrus, the right and left heads of the caudate nucleus, the dentate region of the cerebellum, and the right superior lobule of the cerebellum. In the left middle temporal gyrus and left and right frontal white matter, the LCMRGlc was significantly increased compared with controls. After a Bonferroni correction for multiple comparisons, however, none of these differences between patients with MND and controls is significant.

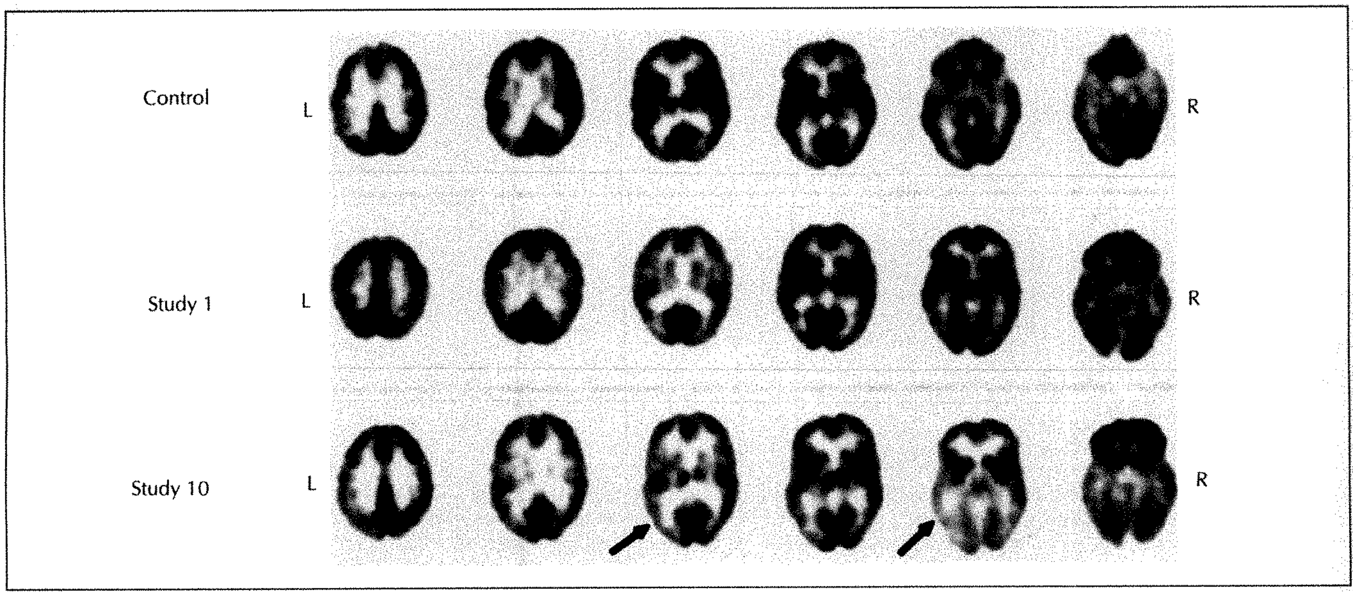

Fig 1.—*Fludeoxyglucose F 18 (^{18}F-fluorodeoxyglucose) positron emission tomographic images obtained in this study. Six cross-sectional emission tomographic images from the level of the tentorium to over the convexity are shown. Images are oriented such that left is the subject's left. Images of an age-matched control, study 1, and study 10 (Table 1) are shown. No obvious abnormalities are noted in the control or study 1 images. Study 10 images show a slight reduction of fludeoxyglucose F 18 uptake in the posterior parietal regions, particularly on the left side (arrows).*

rus were used to examine the effects of progressive neurologic deterioration on LCMRGlc. Motor strength and reflex determinations for the patients with MND as well as controls were plotted vs the mean LCMRGlc values. When the mean weighted normalized LCMGRlc of the precentral gyrus was compared with motor strength, we observed that with increasing weakness there was an associated reduction in LCMRGlc for all extremities (Fig 2, top left and top right). For the middle frontal gyrus, however, weighted normalized LCMRGlc values were increased when motor weakness was most profound (Fig 2, middle left and middle right). This particular trend was noted in all extremities. When LCMRGlc was correlated with the deep tendon reflexes, there was inconsistent change in the precentral gyrus for the upper and lower extremities. However, when weighted normalized LCMRGlc values were correlated with the deep tendon reflexes in the middle frontal gyrus, there was a progressive increase in metabolism with progressive UMN involvement (Fig 2, bottom left and bottom right). Spearman Rank-Order

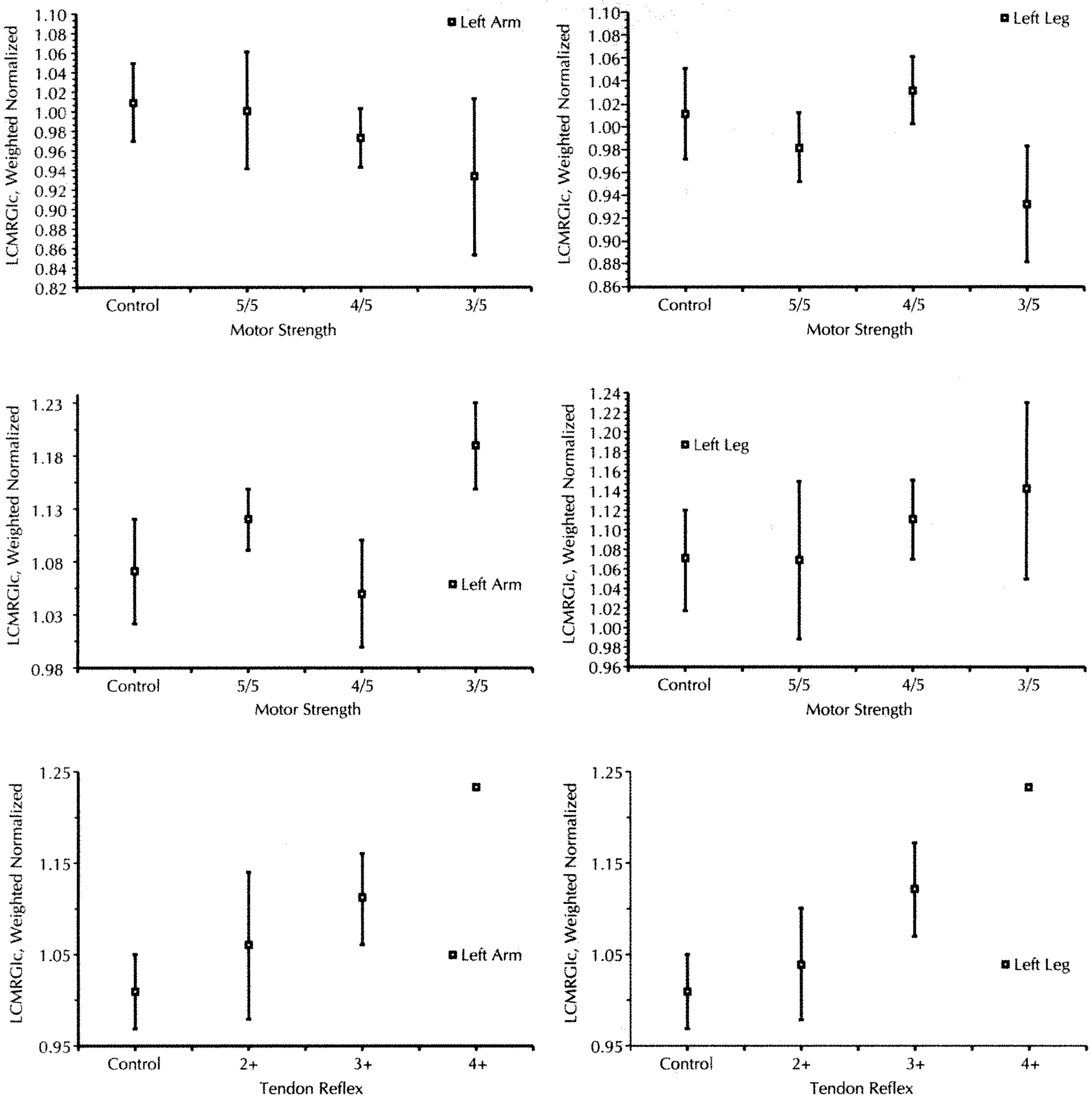

Fig 2.—*Graphic representation of weighted normalized local cerebral metabolic rate of glucose (LCMRGlc) values for the control subjects compared with those of patients with motor neuron disease with (mean±1 SD) objective neurologic assessment of motor strength and deep tendon reflexes in patients with motor neuron disease. The precentral gyrus (top left and top right) and the middle frontal gyrus (middle left, middle right, bottom left, and bottom right) were used to examine the effects of progressive neurologic deterioration on LCMRGlc. When the LCMRGlc of the precentral gyrus is compared with motor strength, it is observed that with increasing weakness in the left arm (top left) and left leg (top right), there is an associated reduction of LCMRGlc. A similar pattern is noted for the right arm and right leg. For the middle frontal gyrus, however, LCMRGlc values were increased when motor weakness was most profound. This particular trend is found in the left arm (middle left), left leg (middle right), right arm, and right leg. When LCMRGlc is correlated with the deep tendon reflexes, there is inconsistent change in the precentral gyrus for the upper or lower extremities. When LCMRGlc values are correlated with the deep tendon reflexes in the middle frontal gyrus, there is progressive increase in metabolism with progressive upper motor neuron involvement (deep tendon reflexes, 3+ or greater) (bottom left and bottom right). This particular finding is noted in all extremities.*

Correlation analysis was also performed to examine the effects of duration and severity of illness on LCMRGlc. There was a significant correlation ($P<.05$) with duration of illness on the LCMRGlc values in the medial superior frontal gyrus, superior lobule of the cerebellum, and frontal white matter. Severity of illness correlated significantly with LCMRGlc values in the superior parietal lobule, dentate of the cerebellum, and superior lobule of the cerebellum. If a Bonferroni correction for multiple corrections is performed, however, no significant correlation with regional LCMRGlc values and duration or severity of illness is noted.

Three subjects underwent repeated studies approximately 1 year after the initial study. Despite worsening of their clinical condition (Table 1), no significant reduction in LCMRGlc was observed for any ROI.

COMMENT

This study was performed to examine the relationship between LCMRGlc and the neuropathologic findings of neuronal loss in motor and motor association cortices in patients with MND. Previous studies with FDG and PET in patients with ALS showed widespread reductions in LCMRGlc, even in brain regions not considered to be associated with motor function.[31-33] Our study did not show such LCMRGlc reductions in motor or nonmotor regions.[34]

The difference between our results and those of other investigators[31,32] may be due to the nutritional status of the subjects at the time of the FDG-PET study. Subjects in this particular study were carefully selected to avoid the introduction of variables of nutritional status, ketosis, or respiratory compromise. It is well known that starvation increases ketone utilization by the brain of D-β-hydroxybutyrate and acetoacetate.[35,36] It has been noted in this situation that up to 60% of oxygen consumption can be explained by metabolism of D-β-hydroxybutyrate and acetoacetate as a metabolic substrate.[35,36] The nutritional status of subjects with MND can play an important role in altering the measurement of glucose metabolism with PET. In our study, however, there was not a significant effect, because all study subjects had a normal nutritional status.

Age matching of the control group should eliminate the effects of aging on LCMRGlc in this comparison study. Previous investigations[37-41] have shown inconsistent age-related effects on LCMRGlc. Studies conducted in our laboratory have shown certain age-related regional reductions in LCMRGlc.[37] Yoshi et al[38] recently described a large population of healthy subjects and noted age-related effects on LCMRGlc. However, when atrophy and brain volume effects were controlled, no significant age-related effects were observed.[38]

Our study also tested the sensitivity of glucose metabolic measurements in the identification of selective neuronal cell loss, which has been well described in MND. The neuronal changes of ALS were first described in mid-1869 by Charcot and Jeffrey.[42] Numerous early pathologic studies described selective degeneration of spinal motor neurons, cranial nerve motor nuclei, and the corticospinal tract. The first description of cerebral cortical degeneration localized to the prerolandic cortex was by Pierre Marie in 1883.[3] More recent pathologic studies of the brain have included newer histochemical techniques,[1,22,43,44] which have shown more widespread neuronal degeneration in the postcentral, frontal, and parietal gyri. General necropsy has failed to reveal abnormalities outside the nervous system.

Histopathologic abnormalities observed in ALS include loss of large pyramidal cells in motor cortex, corticospinal tract degeneration, and loss of Betz's and pyramidal cells from the fifth layer of motor cortex.[1,43-45] With the use of histochemical preparations (ie, Marchi preparations), degenerating fibers have been observed in the paracentral lobule and the postcentral, frontal, temporal, and cingulate gyri.[1,46] Gliosis can be observed in the thalamus, globus pallidus, ansa lenticularis, and hypothalamus. In the brain stem, degeneration and depletion of neuronal cell bodies in motor nuclei (rarely oculomotor) and cortical spinal tracts have been observed.[46] Spinal cord disease includes neural cell changes in motor nuclei of anterior horn cells and corticospinal tract degeneration.[1] Nerve roots often appear fibrosed with loss of axons and myelin. Even as late as 1982, Hughs[1] commented that despite a considerable amount of investigation, a full range of neuronal cell body changes observed in the cortex have not been examined adequately. The emerging consensus, however, is that ALS is a neuronal degeneration involving anterior horn cells, motor cortex, corticospinal tracts, and motor association cortices.[1,47]

Specific measures of the neurologic examination were correlated with weighted normalized LCMRGlc. As noted in Fig 2, consistent effects were observed between LCMRGlc and motor strength or reflex changes for the precentral and middle frontal gyri. These brain regions are known to be maximally affected histopathologically in ALS. With increasing weakness, the LCMRGlc of the precentral gyrus declines (Fig 2). This particular finding is consistent with observations by Munsat et al[7] of symmetric and linear loss of motoneurons in ALS over time. In the middle frontal gyrus, however, with increasing weakness, the LCMRGlc increases (Fig 2). This finding may represent increasing metabolic activity of motor association cortex in response to primary loss of pyramidal cells. This relationship is also observed when tendon reflex changes are correlated with LCMRGlc. In the precentral gyrus, the LCMRGlc may remain unchanged or decrease with heightened reflexes (ie, UMN involvement).

Amyotrophic lateral sclerosis involves a combination of UMN and LMN dysfunction, and abnormally increased reflexes are related to UMN dysfunction. It is difficult to quantitate UMN involvement in ALS.[48] Investigators have judged spasticity and plantar responses by various means; however, motor weakness from LMN involvement confounds such quantitative attempts.[17,18,49] In the middle frontal gyrus, UMN involvement was associated with an increase in LCMRGlc. In a manner analogous to LCMRGlc changes observed with motor strength, increased metabolism is observed in the motor association cortex as reflexes become more pathologic. Again, this may represent increased neuronal activity in the motor association cortex in response to primary motor neuron and pyramidal cell loss.

Severity of disease did not correlate with LCMRGlc. A rating scale was devised (see "Statistical Analysis" section) to allow for this analysis. Various authors have described and validated reliable testing procedures that allow for quantitative assessment of motor neuron loss,[17] the best known example being the Tufts Quantitative Neuromuscular Exam.[48] For the purposes of this study, however, a more simple global assessment of disease severity that incorporated both UMN and LMN findings and functional status was required. The duration of disease seems to have little effect on weighted normalized LCMRGlc values. This is not an unexpected finding, as many patients have a rapid and precipitous decline in function. In fact, the most severely affected patient in our study had the shortest duration of illness. We believe that in these carefully selected patients with good nutrition and hydration, the possibility of systemically altered substrate metabolism effecting LCMRGlc is unlikely.

An interesting observation in this study was increased LCMRGlc in white-matter regions. Pathologic studies describe changes in subcortical regions that correspond to degeneration of white-matter tracts corresponding to pyramidal cell loss.[43,44,46,50] Recently, in patients with ALS, focal areas of increased signal intensity on T_2-weighted magnetic resonance imaging scans were noted extending from the motor cortex through the corona radiata and into the internal capsule.[51] Altered LCMRGlc appears to coincide with these pathologic and anatomic imaging abnormalities.

In conclusion, our study does not suggest widespread neuronal metabolic dysfunction in patients with MND.

Much like FDG-PET studies in patients with Parkinson's disease, no substantial consistent focal metabolic abnormality was observed.[52-54] Numerous investigations with the use of FDG-PET in patients with Parkinson's disease have failed to show substantial alteration in glucose metabolism in the striatum. The reason for this is most likely the small population of nigrostriatal neurons used in dopaminergic neurotransmission compared with the total synaptic population of the striatum. Measurement of cerebral glucose metabolism with FDG-PET is not sensitive enough to loss of dopaminergic synapses compared with other synaptic populations. Analogously, few specific neurons are lost in MND compared with other metabolically active cells; therefore, the loss of a specific subpopulation does not greatly alter the regional glucose metabolism. Furthermore, patient selection, nutritional status, and severity of disease may be responsible for the difference in FDG-PET results now described in the literature for MND and ALS.

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Early Predictors of Poor Outcome in Congenital Fiber-Type Disproportion Myopathy

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• **We report the cases of eight children with histologic findings in the muscle of congenital fiber-type disproportion myopathy. Five had severe muscle weakness at birth; three of them died at 6 months, 18 months, and 6.5 years of age, respectively, and the other two are ventilator dependent and need total care at 2.5 and 4 years of age. The five children with severe weakness at birth had profound respiratory muscle weakness and needed assisted ventilation since early infancy. They also had severe facial and bulbar muscle weakness that required tube feeding, and four had gastrostomy. Ptosis and marked external ophthalmoparesis were also noted. Our study shows that the presence of the above constellation of signs at birth or in early infancy is a predictor of a high rate of mortality in infancy and poor developmental outcome in the survivors.**

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Although a great variability in the clinical course and outcome has been reported in children with congenital fiber-type disproportion myopathy (CFTDM),[1-3] some infants present severe weakness at birth or in early infancy. In this latter group of infants, a high mortality has been reported among those who exhibit hypoventilation and severe bulbar muscle weakness.[4] The clinical characteristics, associated with poor outcome in infancy and early childhood, although previously noted, have not been well recognized. In our study, five of eight children with CFTDM had clinical signs that were predictors of poor developmental outcome and high mortality rate in infancy.

REPORT OF CASES

Eight children (six girls and two boys) were followed up since birth (Table). Five patients (cases 1 through 5) had severe signs of muscle weakness since birth. They needed assisted ventilation in the first 3 to 4 weeks of life and tracheostomy later on. They all had external ophthalmoparesis and four had ptosis. The facial and bulbar muscles were markedly affected, they were unable to close the lips, and the mouth was open all the time. Gavage feeding and frequent suctioning of oral secretions were necessary, and four of them required gastrostomy. Three children (cases 6 through 8) had moderate signs of muscle weakness at birth, they all had moderate respiratory distress, with mild intercostal retractions, fatigue while feeding, and excessive drooling.

Clinical Course and Outcome

CASE 1.—This child showed no signs of motor development after birth. He remained profoundly weak, with minimal spontaneous motor activity and died of respiratory infection at 6 months of age.

CASE 2.—The course of this patient was similar to that of the patient in case 1. She was able to move the distal parts of her limbs but had no visible motor function of the hips, shoulders, trunk, or neck. She died of respiratory infection at 18 months of age.

CASE 3.—This child remained hospitalized during her first year of life because of severe respiratory weakness. Later, she required assisted ventilation only while sleeping. She was able to swallow soft food, to sit with support, and to move around in her electrical wheelchair. She died of respiratorory infection at 6.5 years of age.

CASE 4.—This patient is 2.5 years of age. In a supine position, he slowly reaches out and holds a rattle for brief moments. He can fully flex and extend the ankles, knees, wrists, and elbows against gravity but there is only a trace of movement at the hips, shoulders, trunk, and neck. Ophthalmoparesis, ptosis, and facial and bulbar muscle weakness are moderate to severe. All reflexes are decreased.

CASE 5.—At 4 years of age, this child is wheelchair bound. She has moderate head control, rolls over, sits with help, reaches out, and holds objects. She has mild facial weakness, minimal drooling, and says a few words.

CASES 6 **Through 8 (Moderate Cases).**—The patients in these cases have had similar courses. They had no ptosis or ophthalmoparesis and did not need tracheostomy or gastrostomy. One patient had to be fed via gavage for about 1 year. Their speech is dysarthric and their motor development has been very slow. They need some assistance in daily living activities, they walk slowly and waddlingly, and they use the handrail to walk upstairs. They cannot jump or run.

Laboratory Reports

All eight children had normal creatine kinase values, computed tomographic head scans, and/or magnetic resonance imaging head scans. Nerve conduction velocities were normal. Electromyogram showed small motor unit action potentials of short duration and absence of fibrillations and positive waves. Muscle biopsy from the quadriceps femori was performed in all infants in the first 4 months of life. Muscle fibers revealed no structural abnormalities or fiber-type predominance. Five percent to 15 % of fibers (types I and II) had the nucleus in the center. Type I fiber size in the children with severe conditions (cases 1 through 5) was less than 5 to 8 μm (normal=8 to 15 μm), and they were 40% to 60% smaller than type II fibers. In the children with moderate

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Major Clinical Features in Eight Patients With Congenital Fiber-Type Disproportion Myopathy*

	Patient No.							
	1	2	3	4	5	6	7	8
Sex	M	F	F	M	F	F	F	F
↓ Fetal movement†	+	+	+	+	+	+	+	+
Intubation	Birth	3 wk	Birth	4 wk	1 d	–	–	–
Tracheostomy, mo	2	4	3	5	1	–	–	–
Gavage feeding	+	+	6 mo‡	+	+	1 y‡	–	–
Gastrostomy	2 mo	2 wk	–	4 mo	5 mo	–	–	–
Ophthalmoparesis	+++	+++	+++	+++	+	–	–	–
Ptosis	+	+	+	–	–	–	–	–
Facial weakness	+++	+++	+++	+++	+++	++	++	++
Dead	6 mo	18 mo	6.5 y	–	–	–	–	–
Age at last visit, y	. . .	. . .	. . .	1.5	3	7	9	9.5
Ventilator dependent	. . .	. . .	. . .	+	+	–	–	–

*Plus sign indicates present; two plus signs, moderate; three plus signs, severe; and minus sign, not present. Patients in cases 1 through 3 were brother and sister. Patients in cases 6 and 7 are sisters. Their father had bilateral esotropia.

†Downward pointing arrow indicates fetal movements were decreased.

‡Age at which gavage feeding was discontinued.

conditions (cases 6 through 8), the type I fibers were 5 to 10 µm and 30% to 40% smaller than type II. The size for type II fibers was 8 to 18 µm in all eight infants. The child in case 6 underwent repeated quadriceps muscle biopsy at 6 years of age. Twenty percent of type I fibers were still very small (10 to 15 µm) and angulated. Thirty percent to 40% of type II fibers were large (>90 µm). Muscle histologic features in the mothers of cases 4 and 8 were normal.

COMMENT

Early reports suggested that CFTDM was a benign myopathy and that affected infants would improve their muscle strength with time.[1-3] The clinical findings reported on those children were more consistent with mild to moderately severe cases. They had no cranial nerve abnormalities, ptosis, or ophthalmoparesis. In attempting to correlate the muscle histologic findings with the severity of weakness and outcome, it was thought that the absence of central nucleus in the muscle fibers carried a more benign, nonprogressive course.[3] However, in a recent report[5] of four infants (two with 50% or more fibers with central nucleus and two with only 10% of fibers with central nucleus), two died in early infancy (one of each category). All had marked bulbar muscle weakness, ophthalmoparesis, and ptosis. The authors of that report[5] found that the severity of muscle weakness and hypoventilation at birth predicted the outcome more accurately than the histologic findings in the muscle. Another study of three infants with CFTDM who died before 1 year of age also confirmed the observations that when the bulbar and facial weakness and ophthalmoparesis are severe, they carry a poor prognosis for survival beyond infancy.[4] Our eight children had a normal percent of muscle fibers with central nucleus and they all fall in the description of fiber-type disproportion with type I hypotrophy (smallness) without centronuclei. The five children (Table) with severe weakness had, in general, smaller type I fibers than the three children with moderate weakness. They also showed more severe facial-bulbar muscle weakness, ophthalmoparesis, and ptosis. None of the children with moderate conditions had ptosis or ophthalmoparesis and they did not require tracheostomy or gastrostomy. Type I muscle fiber predominance, commonly seen in CFTDM,[6] was not present in any of our patients' muscle abnormalities. The absence of this histologic finding is of unclear significance to us.

We would agree with Lo et al[5] that our five infants with severe CFTDM could not be clinically distinguished from infants with severe congenital centronuclear myopathy and that it is likely these two clinical entities represent a different state or degree of the same abnormality in the developing muscle fibers. Our study indicates that it is possible to predict the outcome in early infancy in severely affected children with CFTDM. Further analysis of the muscle fiber size in a larger number of patients is necessary to ascertain that there is a correlation between degree of smallness of type I fibers and severity of muscle weakness.

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Vascular Event Rates in Patients With Atherosclerotic Cerebrovascular Disease

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• The purpose of this study was to review data from published cerebrovascular studies to determine if it is possible to predict, based on clinical manifestations (eg, cervical bruit, transient ischemic attack, or stroke) of cerebrovascular atherosclerosis, the annual probability of having a stroke, as well as to determine and discuss the methods used in calculating and reporting vascular event rates. This overview analysis reveals that the annual stroke rates are as follows: for asymptomatic carotid stenosis, 1.3% (95% confidence interval [CI], 1.0 to 1.6); for transient monocular blindness, 2.2% (95% CI, 1.3 to 3.0); for transient ischemic attack, 3.7% (95% CI, 3.1 to 4.3); for minor stroke, 6.1% (95% CI, 5.7 to 6.6); and for major stroke, 9.0% (95% CI, 8.0 to 9.9). The data analyzed here suggest that a hierarchical profile of worsening clinical characteristics mirrors a hierarchical progression of increasing risk of stroke. These data support the idea that there is a clinical risk profile, in addition to the conventional atherosclerosis risk factor profile, for predicting subsequent stroke.

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There is debate about the relative impact that various factors have on predicting stroke risk. Age and other known risk factors for atherosclerosis, such as hypertension, diabetes mellitus, smoking, and hypercholesterolemia, are generally held to increase the chance of future stroke. Likewise, the presence and degree of arterial stenosis have an almost certain impact on prognosis for future stroke, but the extent is not clearly defined. The implication of various clinical manifestations of cerebrovascular disease, namely, transient monocular blindness (TMB), transient ischemic attack (TIA), and minor and major stroke, is more controversial and yet may be the most clinically relevant since most patients present with symptoms rather than a list of risk factors or a documented stenosis. This issue of how various clinical features affect the expected annual incidence of cerebral infarction is important because it may provide a basis for furnishing reliable, realistic prognoses for patients and for determining whether expensive or risky treatment is warranted in particular subsets of patients. It also may provide a basis for calculating sample size estimates for clinical trials; an error of a few percentage points in the expected outcome event rate produces a huge difference in the estimate of sample size and the length of study that will be required.

While some believe that TMB, TIA, and minor and major stroke identify patients at different risk for future stroke, others believe that they are merely different manifestations of the same underlying pathology and, therefore, should be expected to have similar predictive value for future stroke. It was recently stated, "It is inherently unlikely that there is any qualitative difference between TIA and mild ischaemic stroke patients (indeed there is now evidence that this is true), nor any inherent reason why these two groups should be qualitatively any different from severe ischaemic stroke. . . . As far as one can tell, the subsequent risk of serious vascular events is not very different after TIAs, mild ischaemic strokes, and more major ischaemic strokes . . ."[1]

It seems likely to us that there is a substantial difference in risk for subsequent stroke in patients with a carotid bruit or stenosis, TIA, minor stroke, or major stroke. Pathologically, there is a spectrum of atherosclerosis that progresses from mild to severe. We hypothesize that there is also a clinical spectrum of severity, with a concomitantly increasing risk of ischemic stroke, myocardial infarction, and vascular death as the cerebrovascular atherosclerosis worsens. Consequently, we decided to review published data that might help delineate the relative risk in individuals with varying clinical markers of atherosclerotic cerebrovascular disease, ie, identify a clinical risk profile for future stroke.

MATERIALS AND METHODS

There are many sources of data addressing the issue of rates for vascular events in patients with atherosclerotic cerebrovascular disease. We chose to review the studies[2-40] in Table 1, because they include the major prospective, randomized treatment trials that have been published[8,17,18,20-28,30] plus a few population studies[2,3,16,29,31] and a hospital survey.[13] Our selection was based chiefly, but not exclusively, on studies with substantial numbers of patients who were observed prospectively.

One major difficulty in assessing the risk of stroke is that it is difficult to determine the actual annual rates in various studies because different methods are used in determining and reporting them. In some studies that we analyzed, the data were calculated by life table from which an annual incidence could be extracted

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Table 1.—Annual Vascular Event Rates for Individuals With Various Features of Atherothrombotic Cerebral Vascular Disease*

Population	Reference No.	Subgroups	Duration of Study, y	No. of Patients	Annual Stroke Rate†	SE in Stroke Rate	Annual VD Rate†	SE in VD Rate	Annual Death Rate†	SE in Death Rate
General population	2	General population	5.90	1548	0.58	0.08				
Asymptomatic	2	Bruit	5.90	72	2.53	0.80				
	3	Bruit	6.50	171	1.71	0.40	3.41	0.59	4.94	0.72
	4	Mild stenosis	1.93	230	0.68	0.39	2.30	0.73	2.78	0.80
		Moderate stenosis	1.93	157	1.00	0.58	3.41	1.08	4.12	1.19
		Severe stenosis	1.93	113	2.83	1.15	8.99	2.12	10.65	2.33
	5	Stenosis	1.00	95	2.13	1.50				
	6	Stenosis	7.00	339	0.73	0.18	2.33	0.33	3.96	0.44
	7	Stenosis	1.45	122	2.30	1.15	7.77	2.16	14.41	3.01
	8	Stenosis	2.45	242	1.72	0.54	5.79	1.02	10.74	1.44
	(by sides)	Normal	2.45	85	0.48	0.48				
		Mild	2.45	171	0.00	0.00				
		Moderate	2.45	150	0.82	0.48				
		Severe	2.45	78	1.60	0.92				
TMB	9		6.00	110	2.27	0.61	2.80	0.68	3.72	0.79
	10		2.50	45	1.82	1.29			1.82	1.29
	11		5.37	93	2.12	0.67	4.51	1.01	5.83	1.17
TIA	11		5.37	212	4.33	0.65	4.33	0.65	5.95	0.78
	12		7.80	314	0.63	0.16	1.56	0.26	2.47	0.33
	13		1.00	299	14.78	2.31	0.00	0.00	8.02	1.67
	14		2.28	44	8.80	3.12			6.43	2.63
	15	Aspirin	0.94	63	3.43	2.43	0.00	0.00	0.00	0.00
		Sulfinpyrazone	0.94	61	3.55	2.51	1.76	1.76	1.76	1.76
	16		2.00	198	12.57	1.90			6.75	1.35
TIA plus stroke	17	Aspirin	2.00	88	6.03	1.91	1.15	0.81	1.73	1.00
		Placebo	2.00	90	8.45	2.26	3.45	1.41	4.05	1.53
	18	Aspirin	2.08	101	8.86	2.15	2.94	1.20	3.45	1.31
		Placebo	2.08	102	5.49	1.66	2.91	1.19	3.42	1.29
	19		4.10	188	3.04	0.65	2.31	0.56	3.63	0.71
	20	Aspirin	2.17	290	6.11	1.02	2.45	0.63	2.78	0.68
		Placebo	2.17	139	7.16	1.60	3.80	1.15	4.52	1.26
	21	Aspirin	2.08	442	7.01	0.91	3.15	0.59	4.32	0.70
		Dipyridamole/aspirin	2.08	448	6.05	0.83	3.22	0.60	5.21	0.77
	22	Placebo	4.00	814	3.95	0.36	2.79	0.30	4.06	0.37
		Low-dose aspirin	4.00	806	3.35	0.33	2.82	0.30	3.60	0.35
		High-dose aspirin	4.00	815	3.27	0.33	2.72	0.30	3.66	0.35
	23	Ticlopidine	3.28	1529	3.64	0.28	2.49	0.23	3.71	0.28
		Aspirin	3.25	1540	4.56	0.31	2.41	0.22	4.19	0.30
	24	Medical group	2.00	331	16.15	1.70	2.88	0.77	4.37	0.95
	25	Placebo	3.00	204	5.49	0.99	1.00	0.41	1.50	0.50
		Aspirin	3.00	198	2.99	0.73	0.68	0.34	1.73	0.55
		Dipyridamole/aspirin	3.00	202	3.11	0.73	1.35	0.48	1.87	0.56
	26	Dipyridamole/aspirin	2.00	1250	4.78	0.45	2.84	0.34	4.52	0.43
		Placebo	2.00	1250	7.96	0.59	4.17	0.42	6.67	0.53
	27		4.65	714	7.28	0.51				
		Carotid occlusion	4.65	147	9.16	1.29				
		Asymptomatic	4.65	276	6.50	0.77				
Stroke	28	Aspirin	2.00	253	6.76	1.20	5.64	1.09	6.99	1.22
		Placebo	2.00	252	6.79	1.20	5.22	1.05	7.02	1.22
	29		5.00	222	7.97	0.94			10.25	1.10
	30	Placebo	1.67	220	9.09	1.64	4.82	1.17	10.05	1.73
		Suloctidil	1.67	218	9.51	1.68	1.67	0.68	6.68	1.39
	31		1.00	575	10.44	1.38				
	32	Placebo	2.00	528	10.27	1.04	4.04	0.63	6.46	0.81
		Ticlopidine	2.00	525	8.27	0.93	3.14	0.56	6.50	0.81
Carotid occlusion	33	Asymptomatic major stroke	2.00	38	4.11	2.37			7.05	3.16
	34	Asymptomatic major stroke	3.70	121	7.11	1.35			14.79	2.10
	35	Asymptomatic major stroke	1.38	43	5.24	3.03			10.89	4.45
	36	Asymptomatic major stroke	3.67	359	7.76	0.83			15.40	1.25
	37	TIA minor stroke	3.00	37	5.90	2.41	6.99	2.65	10.50	3.34
	38	TIA minor stroke	5.00	138	2.63	0.64	2.63	0.64	4.90	0.90
	39	TIA minor stroke	2.87	47	9.29	2.81	2.30	1.33	3.10	1.55
	27	TIA stroke symptoms	4.65	147	9.16	1.29				
		Asymptomatic	4.65	276	6.50	0.77				
	40	Asymptomatic	2.60	49	6.86	2.43	17.61	4.19	24.37	5.17

*SE indicates standard error; VD vascular death; TMB, transient monocular blindness; and TIA, transient ischemic attack.

†Annual event rates are given as percent per year.

Table 2.—Aggregate Estimates of Annual Vascular Event Rates for Individuals With Various Clinical Manifestations of Atherothrombotic Cerebrovascular Disease

Clinical Features	Annual Probability, % (95% CI*)		
	Stroke	Vascular Death	All Death
General elderly population	0.6	1.0	. . .
Asymptomatic stenosis	1.3 (1.0-1.6)	3.4 (2.9-4.0)	5.4 (4.7-6.0)
Transient monocular blindness	2.2 (1.3-3.0)	3.5 (2.4-4.7)	4.3 (3.1-5.5)
Transient ischemic attack	3.7 (3.1-4.3)	2.3 (1.8-2.9)	4.0 (3.4-4.6)
Minor stroke	6.1 (5.7-6.6)	3.2 (2.8-3.6)	4.9 (4.3-5.4)
Major stroke	9.0 (8.0-9.9)	3.5 (2.8-4.2)	7.6 (6.7-8.5)

*CI indicates confidence interval.

Table 3.—Aggregate Estimates of Annual Vascular Event Rates for Individuals With Defined Anatomic Severity of Atherosclerotic Cerebrovascular Disease

Anatomic Features	Annual Probability, % (95% CI*)		
	Stroke	Vascular Death	All Death
Asymptomatic stenosis			
Mild	0.4 (0.01-0.7)	2.3 (0.9-3.7)	2.8 (1.2-4.4)
Moderate	0.9 (0.2-1.6)	3.4 (1.3-5.5)	4.1 (1.8-6.5)
Severe	2.3 (0.8-3.7)	9.0 (4.8-13.2)	10.7 (6.1-15.2)
Carotid occlusion	6.6 (5.9-7.4)	4.6 (3.3-6.0)	11.7 (10.4-13.1)
Asymptomatic	6.5 (5.0-8.0)		
Symptomatic	9.1 (6.6-11.7)		
Symptomatic severe stenosis	16.2 (12.5-19.6)	2.9 (1.5-4.4)	4.4 (2.5-6.3)

*CI indicates confidence interval.

in a straightforward manner, eg, the Canadian American Ticlopidine Study.[32] In most studies, especially those in which outcomes in different groups were compared, a total number of events was reported for the patient population of interest during the time it was observed. Annual incidence was calculated from the cumulative incidence over the duration of the study expressed as $-1/a\,[\ln(1-b)]$ where a indicates years followed up; and b, cumulative incidence for the study period. This gives the average annual incidence rate, or number of events per 100 patient-years, which is shown in Table 1. For example, if in a group of patients 50% have a stroke over 5 years of follow-up, the average annual incidence is $-1/5\,[\ln(1-0.5)]$, or 13.96% per year. It is not $50\% \div 5 = 10\%$. While this formula is not perfect, because it assumes that the incidence remains constant with time, it is the best reasonable approximation.

Our aggregate estimates for vascular event rates for each of the several clinical manifestations of cerebrovascular atherosclerosis, shown in Table 2, were calculated from the information in Table 1. For "pure" patient populations (asymptomatic stenosis, TIA, TMB, and carotid occlusion), each group of studies was treated as an aggregate population with summary rates calculated using the same formula, $-1/a\,[\ln(1-b)]$, where a indicates average follow-up time for all patients in that group, and b, total cumulative incidence of events for all studies in that group. Event rates for stroke subtypes, ie, minor and major, were difficult to estimate as minor stroke was never studied as a pure disorder. For these subcategories, studies were used if the majority of patients had suffered a minor[25-28] or major[29-32] stroke. Rates for "mild," "moderate," and "severe" stenoses represent an approximation from the rates reported by Chambers and Norris,[4] and Autret et al[8] for different subsets of stenoses.

RESULTS

Table 1 shows the studies that were reviewed, the cerebrovascular features of the populations studied, and the major vascular outcome event rates that we calculated. The overall rates are shown in Table 2.

The expected average annual cerebral infarction rates for Americans from the Midwest are approximately as follows: 0.07% per year at age 50 years, 0.16% per year at age 60 years, 0.6% per year at age 70 years, and 1.0% per year at age 80 years (J. P. Whisnant, MD, written communication, November 15, 1990). The stroke rate for the average 70-year-old American *male* individual is approximately 1% annually; a useful number to remember for future reference. Similar rates have been reported for other geographic locations. Heyman et al[2] reported an incidence of 0.6% per year in a sample of the general population over 45 years of age. The Oxfordshire data[41] show a crude annual incidence of 1.6 per 1000 (0.16%), and the Framingham data[42] show an incidence of 0.3% per year in a sample of the general population aged 30 to 62 years, followed up over 26 years. Cardiovascular mortality for the average 60-year-old American is 0.4% per year, for the average 70-year-old it is 1.0% per year, and for the average 80-year-old it is 2.5% per year.[43] Similar cardiovascular mortality rates are observed in the United Kingdom.[44]

Approximately 5% of elderly Americans have a cervical arterial bruit. Our analysis shows that patients with asymptomatic carotid disease have approximately twice the risk of stroke and three times the risk of vascular death over that of the general elderly population. The rates for stroke, vascular death, and all death are not significantly different whether carotid disease is defined by the presence of a bruit[2,3] or a documented stenosis.[4-8]

If a patient's atherosclerotic cerebrovascular disease becomes symptomatic, the risk for stroke increases. Transient monocular blindness[9-11] carries a risk of about 2% per year. For patients with TIA,[12-16] it appears to be nearly 4% yearly. It seems to be highest in the first weeks and months after the first TIA than thereafter.[12,15,16]

If patients suffer a minor ischemic stroke,[25-28] their risk for a recurrence increases to about 6% annually. Major stroke[29-32] carries an even worse outlook, with the expected incidence of recurrence rising to 8% to 10% yearly. Vascular and overall mortality rates are not significantly different among various subtypes of cerebrovascular manifestations, with the exception of an increased overall mortality in patients who have suffered a major stroke.

If only placebo-treated patients are analyzed, the event rates are the highest, as expected. In patients with minor stroke, annual rates for recurrent stroke in placebo-treated and actively treated patients are 7.4% and 4.5%, respectively. Corresponding rates for recurrence in patients with major stroke are 10% and 8.6% annually.

The predictive value of anatomic grade of severity of carotid disease and risk of future stroke has been studied only in small numbers of patients and in restricted subgroups. This is shown in Table 3. Patients with an asymptomatic carotid stenosis have an overall risk of about 1.1% each year of having a cerebral infarction. In these patients, some investigators[4,5,8] have found that the risk of stroke correlates with the degree of stenosis, ie, from 0.4% annually for mild stenoses to 2.3% annually for severe (greater than 70% to 75%) ones. Although few data are available regarding the prognosis for patients with greater than 90% carotid stenosis, there is a suggestion that stenoses approaching occlusion generate a high risk for stroke. It even may be that preocclusive asymptomatic carotid stenoses have a worse prognosis than TIA or minor stroke without this degree of stenosis. The data reviewed here suggest that patients with *major stenoses,* defined as greater than 70% to 75%, which are asymptomatic, still have a better prognosis than those with TIA.

The recently reported results of the North American Symptomatic Carotid Endarterectomy Trial[24] provide the first good prospectively collected data on the natural history of symptomatic patients (with transient cerebral or retinal ischemia, or minor stroke) with angiographically documented high-grade stenosis (greater than 70%). During the first 24 months of follow-up, 27.6% of these patients in the "medical group" experienced a stroke. The average annual rate is 16.2%. It is clear that TIA or minor stroke plus high-grade carotid stenosis identifies a group of patients at very high risk for stroke.

If *asymptomatic* individuals with severe carotid stenoses turn out to have a particularly high risk of stroke, and if the several studies of carotid endarterectomy for asymptomatic stenosis that are in progress show a benefit for the operation, the issue of identifying high-grade stenoses in asymptomatic patients may become an important one.

Internal carotid artery occlusion is also a serious affair.[27,33-40] Patients with TIA or minor stroke who have an internal carotid artery occlusion have a risk for stroke of 6% to 7% annually. If their ischemic symptoms continue after identification of the stenosis, the annual risk rises to 9%.[27]

COMMENT

Atherosclerosis is a progressive disease causing increasing stenosis of arteries often resulting in thromboembolism. Common consequences of this process are ischemic stroke, myocardial infarction, and vascular death. Several factors are known to increase the risk of atherosclerosis and its aftermath, eg, hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, increasing age, and family history of atherosclerosis. The contribution of these atherosclerosis risk factors has become progressively clearer as more and more properly conducted studies have been completed in recent years. There is now general agreement that risk profiles for vascular events, based on atherosclerosis risk factors, can be generated.

Establishing risk profiles based on various *clinical manifestations* of atherosclerotic cerebrovascular disease has been more difficult. The reasons for wanting to do so were enumerated earlier. Some investigators believe that symptoms, signs, and evaluation do not identify patients at high risk. One study[45] compared event rates of minor ischemic stroke and TIA in 213 and 184 patients, respectively, observed over a 3-year period. While not reaching statistical significance, stroke and death rates were lower in patients with TIA than in those with minor stroke. The total event rate (stroke plus death) was statistically significantly lower in patients with TIA than in those with minor stroke. It remained lower when TMB was excluded from the TIA group, but the difference was no longer statistically significant. While some investigators believe that TMB is probably a more benign disease than cerebral TIA, the difference between TIA and TMB is probably comparable to the difference between TIA and minor stroke. It seems inconsistent for the authors to split or lump one pair and not the other.

We attempted to obtain our "clinical features" data on prognosis primarily by analysis of studies that chiefly observed patients prospectively. The several studies report various vascular events that accumulated in selected populations. The process of reviewing such a variety of studies to obtain this information is challenging and somewhat problematic.

Methodology for Determining and Reporting Outcome Event Rates

Several problems arose during this analysis regarding the methods used for determining and reporting outcome rates for vascular events. In the various studies, prognosis was estimated in different ways. It was sometimes expressed as an annual event rate, for example, the percent of patients with a TIA or completed stroke who had a stroke or recurrence each year. The event rate was commonly calculated as the number of strokes per 100 patient-years of exposure (for example, 10 strokes per 100 patient-years, or 10% per year). Sometimes, the event rates were calculated from survival curves using the life-table method. In studies in which the primary intent was to assess the effect of various treatments on outcome, the investigators generally compared the total number of events that occurred, the number of patients in the cohort, and an average time during which they were followed up. Others, especially population studies, report cumulative incidence rates for the time studied and, rarely, annual incidence rates. A minority use a life-table method of analysis to calculate yearly incidence rates.

We used the numbers provided to best calculate an *average* annual incidence rate. This was chosen because it was the most consistently available, or calculable from the data available, and, therefore, provides a stable variable by which to compare studies.

We wanted to depict prognosis as a rate because it is handy to summarize the course of disease as a single number that has the value of simplicity and can be compared easily from one study to another. A disadvantage is that the information conveyed is limited and substantial differences in prognosis can be hidden within similar summary rates. For example, 5-year occurrence rates for stroke may follow several patterns (Fig 1). In this example, all patterns have a 5-year stroke occurrence rate of 50% but not the same annual rate. Figure 1 top left, not bottom left, most closely represents a constant incidence rate over time in which the annual incidence may be calculated by $-1/a\ [\ln(1-b)]$, where $a = 5$, the total years followed up, and $b = 50\%$, the cumulative incidence for the study period. Calculated in this manner, the average annual occurrence rate of 13.9% and the summary rate of 50% may fail to express differences of considerable importance. The stroke rate following the onset of TIA appears to follow the depiction in Fig 1 top right, with a higher rate early and a lower rate later on.[12,15,16] Recurrence rates after a major stroke follow a more linear curve,[29,32] as in Fig 1 bottom left. Occurrence rates after discovery of carotid stenosis appear to follow the pattern in Fig 1 bottom right. When interpreting prognosis, one wants to know the likelihood, on the average, that patients with a given condition will experience an outcome at any point in time. When

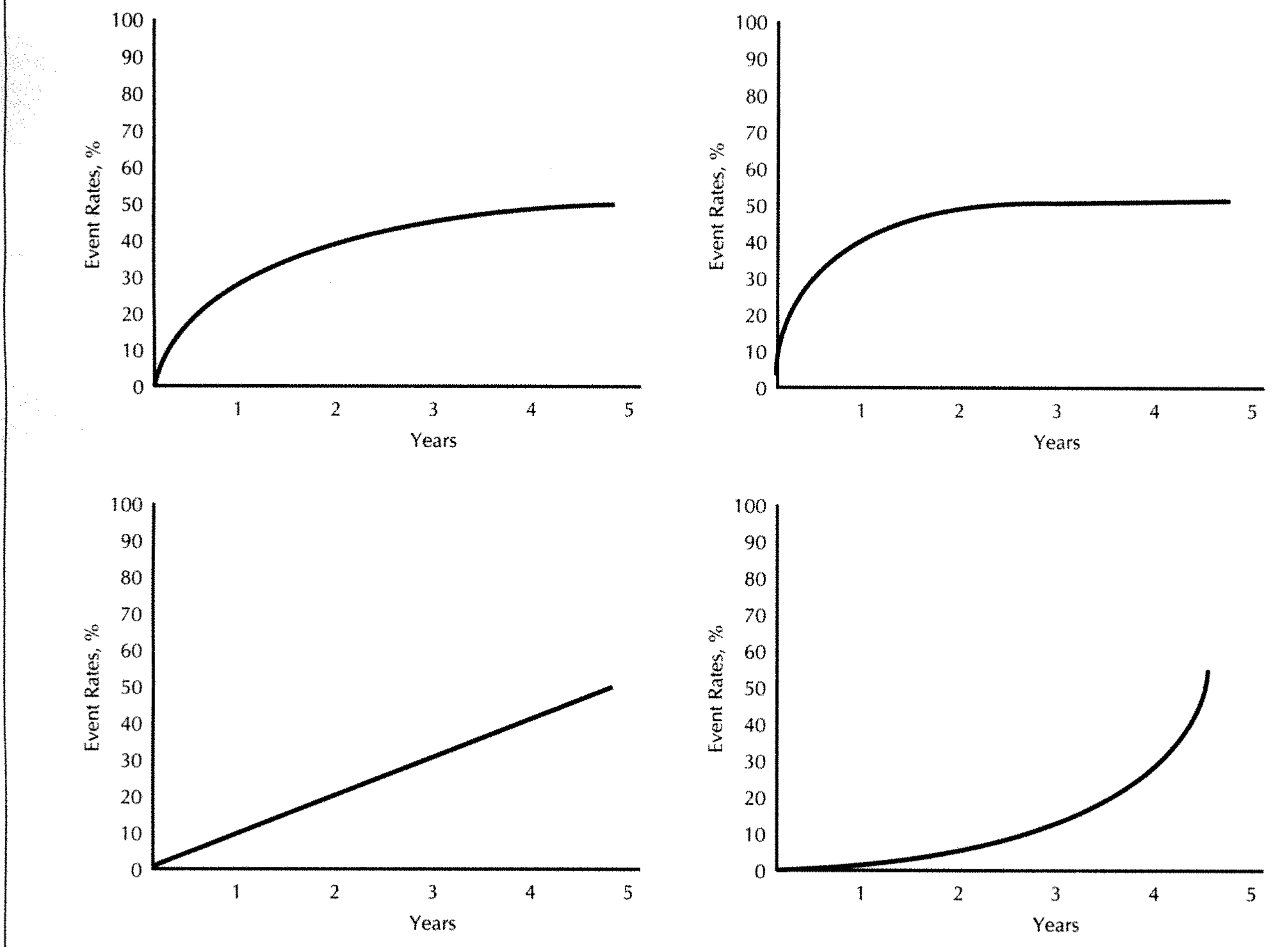


Fig 1.—*Percentage of the patients in a cohort experiencing an outcome event over 5 years of follow-up. Possible patterns of event rates.*

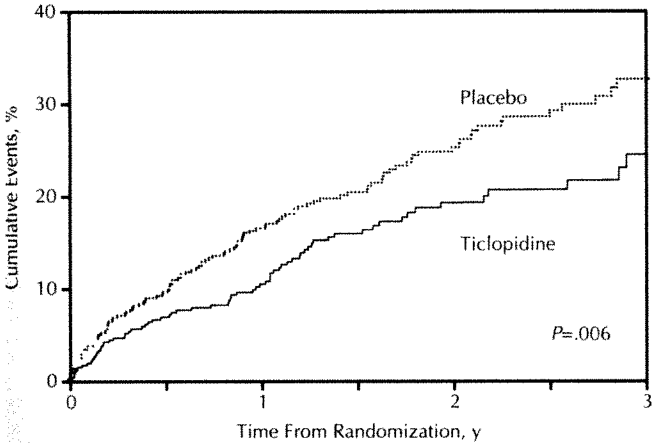
prognosis is expressed only as a summary rate, it does not provide this information precisely. This is most clearly at issue in understanding post-TIA stroke rate because it is nonlinear. The annual stroke rate for these patients is conventionally reported to be higher than we report (approximately, 5% to 6%), reflecting the higher early stroke risk after TIA. Our data summarize the stroke rate over a longer period of time, an average of 3.8 years, and is, therefore, somewhat lower.

The use of incidence rates has other intrinsic problems. Patients followed up for the longest time contribute disproportionately to the final measurement, and, if they are systematically different from patients followed up for a short time, the resulting incidence measurements may be biased. The amount that this bias contributes probably varies from study to study. This is of particular concern for cerebrovascular disease because the incidence rates appear to be nonlinear in some circumstances, as noted above. Comparing studies that have different mean follow-up times is problematic for similar reasons. If, as we think for TIA, the incidence rate declines over time, then annual rates reported from studies with long follow-up times are "falsely" lower. For example, the data of Muuronen and Kaste[12] were collected over a longer period of time than most other studies. This contributes to their lower reported event rates compared with other studies of patients with TIA.

There are methods that make efficient use of all of the important data for presenting information about average time-to-event for any time in the course of a disease. Generating survival curves using life-table analysis is probably the most accurate and efficient means of providing this information. Any outcome that is dichotomous and occurs only once during follow-up can be described in this way. Examples are time to first stroke, or recurrence of stroke. Figure 2 shows the survival curves, or cumulative event curves, for the two large ticlopidine trials. The number of patients at risk at various times is shown to give some idea of the contribution of chance to the observed rates.

Our Overview Analysis

Overview or meta-analysis is a technique that is being increasingly used. One of its advantages is that it uses data from a variety of similar sources and, hence, it can summarize a collective experience with a large number of patients. In this way, highly significant conclusions may be obtainable regarding questions that otherwise may be unanswerable. We chose to use this method because these studies provided a close approximation to natural history data that, as medical and surgical intervention becomes more routine, likely will not be collected in a prospective fashion in the future. Our overview is not a conventional meta-analysis in that it aggregates data from a large num-



P	528	420	335	232	170	110	36
T	525	363	304	208	136	87	25

Patients at Risk

Fig 2.—*Cumulative event-rate curves for fatal or nonfatal stroke. P indicates placebo; T, ticlopidine. (Reprinted, with permission, from Gent et al*[32]*).*

ber of dissimilar studies. In some ways, this is like mixing apples and oranges. However, this may also be a strength of this overview analysis. By comparing various selected populations in different studies, the final aggregate population may be more representative of the population in general. Obviously, the quality of the final information in an overview analysis is directly dependent on the quality of the original studies, a determination that is not always easy to make. Overview analysis does not pool poor data and make the aggregate better. If one is unselective, poor quality and small studies decrease the reliability of the final data. If too much selection is made unsystematically, the final outcome may reflect the bias of the investigators selecting the studies. We chose to be less selective, excluding studies with small numbers and short follow-up times, or those from which the information needed to calculate rates was unavailable, but including a variety of types of studies.

There is a substantial variability in the vascular event rates in Table 1 attesting to the fact that, among the studies, the populations were different, or were studied in different ways. In fact, there are several identifiable differences in the study populations, such as the prevalence of atherosclerosis risk factors. The incidence of peripheral vascular disease varies from 4% to 57%; smoking, 22% to 75%; hypercholesterolemia, 2% to 45%; diabetes, 7% to 31%; and hypertension, 27% to 67%. Heart disease seems more consistently prevalent at about 20%, but different studies "exclude" heart disease or cardioembolism, and they do so by different means.

Age is a powerful risk factor for stroke as the incidence of stroke in all populations increases with age.[29,46] In the Framingham cohort,[28] of 5734 people between 55 and 84 years of age, 472 experienced strokes in 10 years; between ages 55 and 59 years, 5%; and between ages 80 and 84 years, 25% had a stroke in 10 years. The mean age of subjects in most studies was in the 60s and, therefore, was not a large variable. There were two exceptions. The studies of Muuronen and Kaste[12] and Candelise et al[15] were outliers with mean ages of 49.2 and 54 years, respectively. It seems likely that this factor contributed to their lower event rates compared with other studies of TIA.

Certain studies, especially the prospective clinical trials, excluded patients with severe medical illnesses that would be expected to worsen prognosis. At the same time, patients in prospective clinical trials are regularly monitored and treated and they tend to have lower outcome event rates than would be predicted from population surveys. As might be expected, the total mortality rate in unselected patients with major stroke in population surveys[29,31] of 10.3% (95% CI, 8.1 to 12.4) is higher than that in clinical trials[26,30] of 7.0% (95% CI, 5.9 to 8.0). The corresponding stroke rates of 8.4% (95% CI, 7.0 to 10.0) and 9.3% (95% CI, 8.1 to 10.4) are not significantly different. Similarly, as shown in Table 1, the post-TIA stroke and mortality rates in the Rochester (Minn) population study[16] are higher than those seen in the clinical trial reported by Candelise et al.[15]

The time period in which a study is done may also influence the results. Data from Rochester indicate that the stroke rate has declined since its incidence was first studied, although it may have stopped recently. The stroke rate peaked in the early 1950s and declined steadily over the next 25 years.[46] Stroke mortality has declined since 1915.[47]

Another variable in stroke outcome rates may be the inclusion or exclusion of patients with vertebrobasilar disease. The percent of vertebrobasilar events at entry in different studies varied from 0% to 50%. The inclusion or exclusion of patients with "lacunar" disease may also affect prognosis. Additionally, different studies made varied attempts, from 0% to 100%, to document the presence of arterial disease or to exclude cardioembolic sources of cerebral ischemia.

Population studies include treated and untreated patients. For the sake of consistency, we included both the placebo and treated patients in the prospective treatment trials in generating our final estimates. The placebo-treated and actively treated patients are clearly delineated in Table 1. If only placebo-treated patients are analyzed, the event rates are higher, as expected. While outcome data on untreated patients provide a "natural history," they are very limited and it is unlikely that such data will be forthcoming in view of the widespread acceptance of the efficacy of antiplatelet therapy.

In spite of the many difficulties in deriving, from the published literature, accurate values for rates for vascular events in patients with atherosclerotic cerebrovascular disease, the aggregate values in Table 2 appear to be reasonably accurate.

If, as these data suggest, the severity of clinical symptoms is predictive of future outcome, the clinical risk profile is a clinically valuable tool. Whether or not it is a variable, independent from other factors (eg, atherosclerosis risk factors, degree of arterial stenosis), does not detract from its clinical utility. In fact, there is some evidence to suggest that the combined knowledge of all of the above factors is especially valuable. For example, the extracranial/intracranial data[27] suggest that the presence of continuing symptoms in the setting of carotid artery occlusion increases the risk of future stroke over the risk of occlusion alone. Furthermore, data from the North American Symptomatic Carotid Endarterectomy Trial[24] show a much higher than expected 2-year cumulative stroke risk of 27.6% for medically treated patients with TIA or minor stroke and a carotid stenosis of greater than 70%, suggesting again that severe clinical manifestations and severe anatomic disease combine to identify patients at higher risk than predicted by either alone. Thus, the combination of clinical symptoms, presence of vascular risk factors, and anatomic disease provide separate and combined means of identification of patients at risk of stroke.

CONCLUSION

While our estimates of vascular event rates are subject to error from the limitations of the data used, the difficulties in determining event rates from various published studies, and our method of analysis, we believe that we have obtained reasonably reliable aggregate estimates. There is a clear trend toward worsening outcome with increasing severity of clinical characteristics.

The data presented support the idea that there is a clinical risk profile, in addition to an atherosclerosis risk factor profile, for predicting subsequent stroke. The profile appears to be a hierarchical one of worsening clinical features that predict a progressively higher risk for stroke. The greater the number and severity of atherosclerosis risk factors, the greater the risk of stroke. Similarly, the greater the number and severity of atherosclerosis clinical characteristics, the greater the risk of stroke. This may simply be a reflection of the fact that patients with the worst symptoms have the worst atherosclerosis, and, consequently, the highest risk for stroke and other vascular events.

Additionally, a better effort can be made in reporting data from studies, so they can be analyzed by others. The most useful and accurate presentation of data regarding prognosis in patients at risk for cerebral infarction is the life table and event curves showing the number of events, over time, in a certain number of patients at risk.

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Carotid High-Low Flow Ratio Most Accurately Predicts Significant Stenosis

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• The Doppler quantitative carotid blood flow technique is a dynamic, physiologic tool that measures carotid blood flow, velocity, and vessel diameter. A high-low flow ratio that reflects variation in side-to-side carotid flow is calculated. We determined the accuracy of this method for the detection of carotid stenosis in 70 patients with cerebrovascular disease in whom cerebral angiography was the gold standard. The most sensitive measure proved to be high-low flow ratio, which was abnormal in 19 of 23 patients (82.6% sensitivity). The patients with high-grade stenosis had contralateral elevated flow compared with that of patients without high-grade stenosis and age-specific normal subjects. The quantitative carotid blood flow technique reflects compensatory alterations in flow produced by significant carotid disease, with an abnormal high-low flow ratio having the highest positive predictive value. This technique can be used independently to screen for carotid stenosis and as an adjuvant to carotid duplex scanning in the investigation of extracranial carotid disease.

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The investigation of carotid disease in patients with cerebrovascular symptoms frequently includes oculoplethysmography, supraorbital Doppler, and the duplex scan, which delineates stenosis of the carotid bifurcation and its most proximal and distal several centimeters. The quantitative carotid blood flow technique (QFM) provides a physiologic measurement of carotid blood flow, with the use of an A-mode, continuous-wave ultrasound technique to quantify blood flow transcutaneously through the common carotid artery. The blood flow reflects that of both the proximal and the intracranial carotid.

Changes in common carotid blood flow are seen in extracranial carotid disease[1-5] and in intracranial processes, including brain tumor, subdural hematoma, vascular malformation, and middle cerebral artery stenosis.[5,6] The QFM technique has not gained wide applicability, although previous studies have indicated that changes in absolute blood flow, side-to-side variation, and total flow (both carotids) are predictive of carotid stenosis.

We report 70 angiographically documented cases of patients with cerebrovascular disease who underwent QFM studies.

SUBJECTS AND METHODS

Patients were men and women examined at the Francis Scott Key Medical Center, Baltimore, Md, for cerebrovascular disease between January 1986 and March 1989 with cerebral angiography and QFM studies. Seventy-six patients with cerebrovascular disease were identified. Six were excluded, three because of failure to record flow, one because of an interval of longer than 4 months between the angiogram and the QFM, one because of an intervening carotid endarterectomy, and one because of a case of moyamoya. Demographic data and cerebrovascular abnormalities are given in Table 1.

Patients were divided into two groups according to the presence or absence of significant (70% or greater) carotid stenosis by selective intra-arterial angiography. Cerebral angiograms were read by a one of us (C.J.M.), who was unaware of the results of the QFM. The degree of stenosis was determined by measuring the minimum residual lumen (MRL) at the point of greatest stenosis, measuring distal residual lumen (DRL) in the internal carotid artery segment distal to the stenosis, and calculating percentage stenosis according to the following method: percentage stenosis=$1-\mathrm{MRL}/\mathrm{DRL}\times 100$. In all cases, carotid stenosis was extracranial (carotid bifurcation); there were no cases of significant tandem intracranial lesions. Group 1 included 23 patients with significant carotid stenosis, and group 2 included 47 patients with less than 70% carotid stenosis. A comparison group of 40 age-matched normal subjects was studied only with the QFM.

The QFM measures carotid blood flow, velocity, diameter, and wall motion. The instrument used (Ultrasonic QFM System 1000, Hayashi Denki, Kawasaki, Japan) has been described elsewhere.[7,8] Briefly, it has an A-mode transducer to track and measure the vessel diameter and wall motion in real time. An angle-independent Doppler ultrasound technique measures the velocity of blood flow at a cross section of the common carotid artery. A computer-assisted program calculates the volume of blood flow. The QFM studies were recorded with the patients and controls awake and in the supine position. Seven measurements were taken on each side; the highest and lowest values were excluded, and the remaining five values were averaged. The QFMs were scored positive (abnormal) if the high-low flow ratio was greater than 1.25. The high-low flow ratio was calculated by dividing the flow on the higher side by that on the opposite side.

We compared carotid flow, velocity, diameter, and wall motion between the carotid arteries in each group and between the groups. For comparison, we designated arteries as ipsilateral or contralateral. For group 1, the artery with the highest-grade stenosis was ipsilateral, corresponding to the symptomatic hemi-

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Reprints not available.

Table 1.—Patient Population*

					Clinical Presentation, No.			
			Age, y			TIA		
Group	N	Sex, No. M/F	Mean	Range	Infarct†	VB	Carotid	Asymptomatic (Bruit)
Significant carotid stenosis	23	17/6	62	44-76	10	0	12	1
Nonsignificant carotid stenosis	47	30/17	61	32-86	16	10	21	0
Controls	40	32/8	62	32-80	. . .	. . .	. . .	. . .

*TIA indicates transient ischemic attack; VB, vertebrobasilar.
†All in carotid distribution.

Table 2.—QFM Values for Patients and Controls*

	Significant Carotid Stenosis			Nonsignificant Carotid Stenosis			
	Ipsilateral Carotid	Contralateral Carotid	*P*	Ipsilateral Carotid	Contralateral Carotid	*P*	Controls
Flow, mL/s	5.99±1.76	10.82±3.29	<.001	7.89±1.77	8.24±2.08	NS	8.56±1.54
Velocity, cm/s	10.52±3.54	18.86±6.55	<.001	13.85±4.13	14.25±4.48	NS	17.51±3.73
Diameter, mm	8.66±1.20	8.71±1.28	NS	8.65±1.07	8.72±1.06	NS	7.95±0.70
Wall motion, mm	0.45±0.21	0.53±0.17	NS	0.45±0.19	0.47±0.18	NS	0.46±0.13

*Ipsilateral was considered the side of the highest-grade stenosis and/or the side of the symptomatic hemisphere; it was the right carotid for the vertebrobasilar group and controls. Contralateral was considered the opposite carotid. QFM indicates quantitative carotid blood flow; NS, not significant. Values are mean±SD.

sphere or to the bruit in all cases except case 15, in which there was a right occipital infarct. For group 2, the ipsilateral artery was referable to the symptomatic hemisphere. Ten patients in group 2 had vertebrobasilar transient ischemic attacks, and within this group there was no statistically significant difference between the right and left carotid blood flow. The same held true for the normal subjects. We therefore chose the right carotid as the comparison artery for analysis in the 10 patients with vertebrobasilar transient ischemic attacks and for the normal subjects.

To compare the means of the values of the ipsilateral sides vs the contralateral sides, *t* tests for matched samples were used. For comparisons between groups, *t* tests for two sample means were performed. To reduce the probability of a type I error (due to multiple comparisons), a $P<.001$ was required for significance.

RESULTS

Group 1 patients had statistically significant reduced flow and velocity measurements in the ipsilateral carotid artery as compared with the contralateral carotid ($P<.001$) (Table 2). Diameter and wall motion did not differ significantly from side to side. For group 2, flow, velocity, diameter, and wall motion did not differ significantly between the ipsilateral carotid and the contralateral carotid (Table 2).

There was a significant reduction in flow ($P<.001$) (Fig 1) in group 1 when the ipsilateral carotid arteries of groups 1 and 2 were compared. There was an elevation of contralateral carotid blood flow ($P<.002$) (Fig 2) and velocity ($P<.001$) in group 1 as compared with group 2. Diameter and wall motion were not significantly different. Group 1 had significant reductions in ipsilateral flow ($P<.001$) and significant elevation of contralateral flow ($P<.001$) as compared with controls (mean flow, 8.5 mL/s). Group 2 did not differ significantly from controls (Fig 3).

The frequency distribution of the high-low flow ratios in groups 1 and 2 is shown in Fig 4; there was a significant difference at $P<.001$. With the use of 1.2 as the upper limit of a normal flow ratio, 19 of 23 patients with high-grade stenosis, of whom nine had complete occlusions, were detected (mean ratio, 1.91; sensitivity, 82.6%). Four patients had high-grade stenosis (three with complete occlusions) not detected by QFM (82.9% specificity). One of these had 95% stenosis of the internal carotid artery with a proximally situated bifurcation, which may have resulted in a flow measurement of the external carotid artery. With the use of 1.4 as the cutoff point, 16 of 23 patients with high-grade stenosis were detected (sensitivity, 69.6%); however, no false-positive results occurred (specificity, 100%) (Table 3). A flow ratio of greater than 1.4 was highly predictive of high-grade stenosis (positive predictive value, 100%).

COMMENT

We have shown a significant reduction of common carotid blood flow ipsilateral to high-grade carotid stenosis, with elevation of flow on the contralateral side, consistent with collaterization across the circle of Willis. This technique represents an easily accessible, inexpensive way to measure cerebral circulation patterns indirectly in patients with known or suspected cerebrovascular disease.

In 1975, Olson and Cooke[9] first described the transcutaneous ultrasound technique for measuring the diameter, velocity, and blood flow of the human carotid artery in normal subjects. Borodzinski et al[3] described the technical limitations in 1976; the major problem was determining the angle between the direction of the ultrasonic beam with respect to the vessel. Borodzinski et al described a technique in which the transducers were mounted in the same probe, and they were able to determine the angle of incidence accurately. After these early efforts, others refined the ultrasound technique and applied the principles to a variety of clinical situations.[4,5,7,8,10-12] Uematsu et al[5] recommended that the criteria for an abnormal volume flow study include an absolute decrement in flow (less than 6

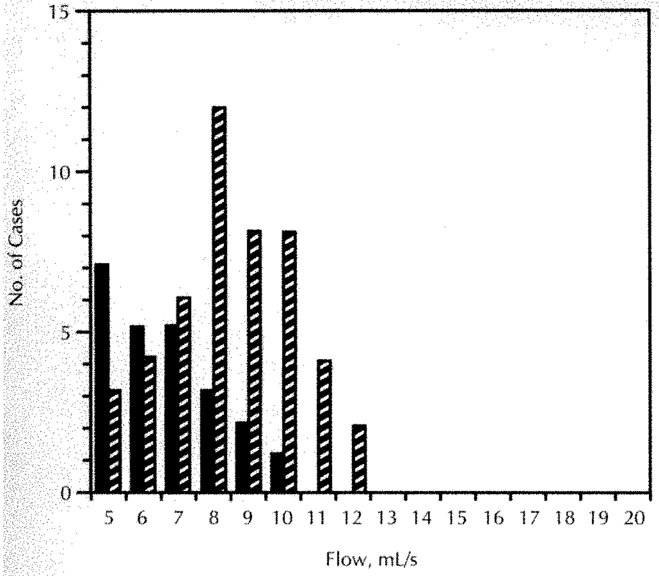

Fig 1.—*Frequency distribution of ipsilateral carotid flow in group 1 (closed bars; significant carotid stenosis; mean flow, 5.99± 1.76 mL/s) and group 2 (hatched bars; nonsignificant carotid stenosis; mean flow, 7.89± 1.77 mL/s).* P<*.001.*

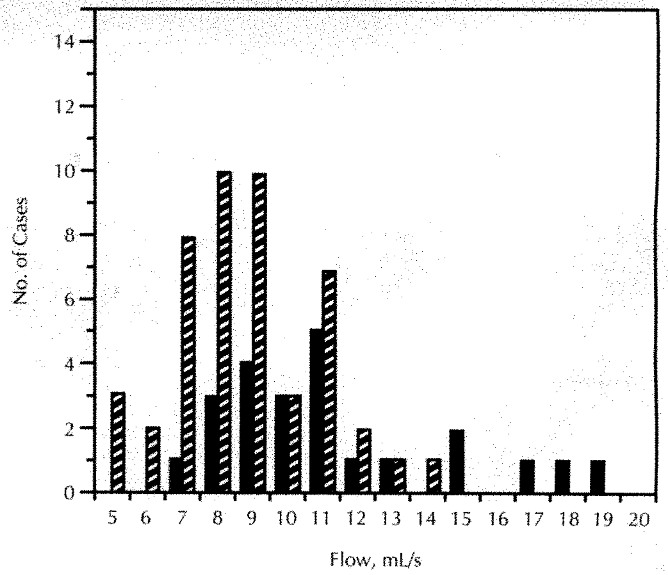

Fig 2.—*Frequency distribution of contralateral carotid flow in group 1 (closed bars; mean flow, 10.82±3.29 mL/s) and group 2 (hatched bars; mean flow, 8.24±2.08 mL/s).* P<*.002.*

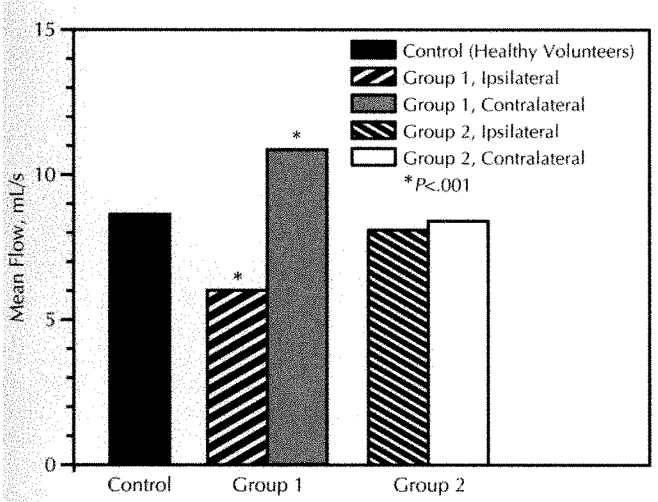

Fig 3.—*Mean carotid blood flow in groups 1 and 2 as compared with that in controls.*

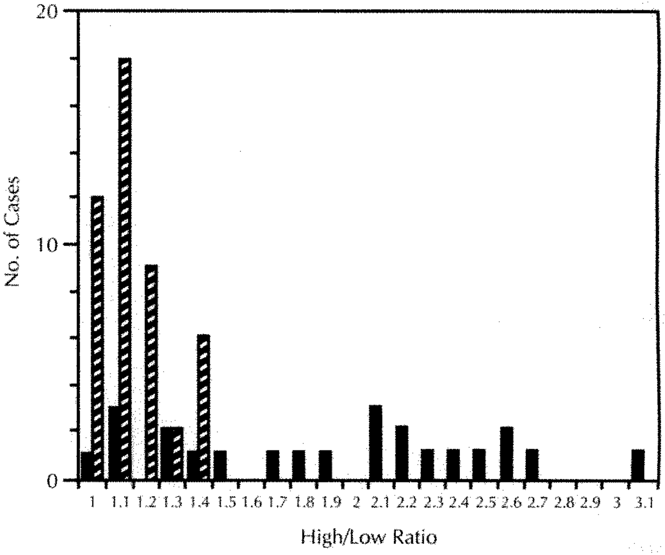

Fig 4.—*High-low ratio in group 1 (closed bars; mean, 1.91±0.60) and group 2 (hatched bars; mean, 1.14±0.13).* P<*.001.*

Table 3.—Comparison of Validity of QFM in Identifying Carotid Stenosis With Abnormal Flow Ratio of 1.25 vs 1.45*

	Flow Ratio >1.2		**Flow Ratio >1.4**	
	Angiogram Positive	**Angiogram Negative**	**Angiogram Positive**	**Angiogram Negative**
QFM positive, No.	19 (A)	8 (B)	16 (A)	0 (B)
QFM negative, No.	4 (C)	39 (D)	7 (C)	47 (D)
Sensitivity (A/[A+C]), %	82.6		69.6	
Specificity (D/[B+D]), %	82.9		100.0	
Positive predictive value (A/[A+B]), %	70.4		100.0	
Negative predictive value (D/[D+C]), %	90.7		67.0	

*QFM indicates quantitative carotid blood flow.

Table 4.—Cerebral Angiogram and QFM Values in 70 Cases of Cerebrovascular Disease*

			Angiogram Stenosis, %		QFM Flow, mL/s		QFM Velocity, cm/s		
Patient	CVD	Ipsilateral Artery	R	L	R	L	R	L	H/L Ratio
				Group 1					
1	TIA	L	MIN	>70	8.93	4.63	16.67	8.41	1.9
2	TIA	R	100	>90	2.71	7.15	5.07	13.44	2.6
3	TIA	R	>95	MIN	8.69	18.19	15.92	34.43	2.1
4	INF	R	100	MIN	6.93	10.98	14.89	26.60	1.5
5	TIA	R	100	MIN	5.68	12.30	7.72	18.58	2.2
6	INF	R	100	55	5.47	14.18	6.90	25.40	2.6
7	TIA	R	100	MIN	4.38	10.67	12.09	9.42	2.4
8	INF	R	100	MIN	6.41	14.38	7.31	24.46	2.2
9	INF	L	MIN	100	9.04	4.35	13.25	6.31	2.1
10	TIA	R	90	75	5.42	7.39	11.44	18.32	1.3
11	INF	L	MIN	95	11.22	5.40	11.09	6.56	2.1
12	INF	L	MIN	99	9.46	7.33	19.75	16.35	1.3
13	TIA	R	90	50	6.12	10.60	8.39	17.65	1.7
14	TIA	L	64	95	9.39	6.55	11.09	11.74	1.4
15	INF	L	MIN	100	16.88	5.46	23.15	6.77	3.1
16	TIA	L	MIN	100	8.45	3.38	13.89	6.97	2.5
17	Bruit	R	75	None	4.81	8.77	11.08	20.73	1.8
18	TIA	R	95	MIN	7.64	17.34	11.54	26.79	2.3
19	TIA	R	100	MIN	3.92	10.40	12.43	24.78	2.7
20	INF	L	MIN	100	7.96	6.72	14.42	12.66	1.1
21	INF	R	100	MIN	9.61	10.49	13.28	24.90	1.1
22	INF	L	None	100	8.42	8.78	10.85	11.29	1.0
23	TIA	L	MIN	95	6.47	7.39	14.04	16.92	1.1
				Group 2					
24	TIA	R	MIN	MIN	7.91	9.53	12.00	14.29	1.2
25	INF	R	None	MIN	5.61	6.13	16.92	20.61	1.1
26	INF	R	MIN	MIN	7.87	8.03	12.67	14.01	1.0
27	TIA	L	50	60	10.69	10.43	13.66	18.10	1.0
28	TIA	R	MIN	MIN	5.36	5.66	9.57	9.33	1.1
29	TIA	L	MIN	50	9.54	9.13	17.14	16.69	1.1
30	TIA	L	50	MIN	7.80	7.25	9.92	8.76	1.0
31	TIA	R	MIN	MIN	8.68	9.26	10.57	12.52	1.1
32	INF	L	25	MIN	6.17	7.26	10.61	12.72	1.1
33	TIA	L	40	MIN	8.70	7.91	16.00	14.12	1.1
34	INF	R	None	ND	3.75	3.26	7.92	7.04	1.2
35	TIA	L	MIN	MIN	6.72	6.99	14.25	15.58	1.0

(cont)

mL/s per side), a high-low flow ratio between the two carotids of greater than 1.2, or an excessive high mean volume flow.

Changes in absolute flow, velocity, or side-to-side differences have been investigated as measures useful in predicting carotid stenosis. Decrements in flow have consistently been demonstrated ipsilateral to carotid stenosis,[1,2,4,5,11,13] with the best correlation occurring in patients with greater than 70% to 80% stenosis.[1,2,5] We have demonstrated statistically significant ipsilateral reduction in flow and emphasize the contralateral elevation in patients with significant carotid stenosis. Because of considerable variation in absolute carotid flow, we found the flow ratio (reflective of side-to-side differences) to be most predictive of significant stenosis. Uematsu et al[5] recommended 1.2 as the upper limit of a normal flow ratio and reported gradations of the flow ratio (1.3 in 21% to 40% stenosis, 2.1 in 41% to 70% stenosis, 2.6 in 71% to 90% stenosis, and 4.2 in 91% to 100% stenosis). In our patients, 11 had a flow ratio of 1.3 to 1.4, including eight with less than 70% stenosis and three with greater than 70% stenosis. However, all patients with a flow ratio greater than

Table 4.—Cerebral Angiogram and QFM Values in 70 Cases of Cerebrovascular Disease* (cont)

Patient	CVD	Ipsilateral Artery	Angiogram Stenosis, %		QFM Flow, mL/s		QFM Velocity, cm/s		H/L Ratio
			R	L	R	L	R	L	
36	INF	R	None	None	7.43	7.74	11.00	11.61	1.0
37	TIA	R	None	None	8.52	10.49	19.57	18.18	1.2
38	TIA	R	MIN	MIN	4.14	5.10	6.89	9.46	1.2
39	TIA	R	None	None	9.66	11.10	19.67	24.48	1.1
40	TIA	L	MIN	MIN	7.66	7.80	11.62	11.36	1.0
41	INF	L	ND	MIN	10.26	9.55	20.92	21.92	1.1
42	TIA	R	MIN	None	8.73	8.60	16.77	16.71	1.0
43	TIA	R	MIN	MIN	9.27	8.12	10.42	11.40	1.1
44	TIA	R	MIN	MIN	8.75	8.54	13.04	12.46	1.0
45	INF	L	MIN	MIN	8.13	8.03	17.77	18.70	1.0
46	TIA	R	MIN	MIN	11.01	9.49	10.93	10.58	1.1
47	TIA	L	45	45	6.33	6.35	6.68	6.58	1.1
48	INF	L	MIN	None	7.61	6.17	16.87	12.67	1.2
49	TIA	R	None	None	6.81	8.11	14.62	17.37	1.2
50	TIA	L	None	None	8.97	7.42	14.76	10.05	1.2
51	INF	L	MIN	None	4.86	4.30	7.25	7.55	1.1
52	INF	L	40	60	5.35	4.76	7.59	6.42	1.1
53	TIA	R	MIN	MIN	6.20	7.14	10.05	13.23	1.2
54	TIA	L	None	None	11.54	10.63	22.27	18.84	1.1
55	INF	L	MIN	40	7.54	7.88	14.30	13.62	1.0
56	TIA	R	None	MIN	8.23	9.39	11.02	12.42	1.1
57	INF	R	None	MIN	10.31	10.04	18.17	18.17	1.0
58	TIA	R	None	None	6.89	7.85	10.38	11.27	1.1
59	TIA	R	MIN	MIN	8.35	6.87	19.21	15.89	1.2
60	INF	R	30	MIN	8.50	7.76	19.90	17.93	1.1
61	TIA	R	None	MIN	7.35	7.64	16.38	16.49	1.1
62	TIA	R	MIN	None	6.59	6.78	14.47	14.27	1.0
63	INF	L	None	50	6.96	10.04	12.01	8.25	1.4
64	TIA	R	MIN	ND	9.10	12.28	20.13	24.71	1.3
65	TIA	R	None	25	8.42	10.58	11.66	14.89	1.3
66	TIA	R	MIN	MIN	9.40	13.61	13.46	19.50	1.4
67	TIA	R	None	None	7.45	10.07	14.06	19.44	1.4
68	TIA	L	MIN	MIN	7.71	5.40	14.90	12.89	1.4
69	INF	R	None	45	11.39	7.95	20.45	14.34	1.4
70	INF	L	None	MIN	10.91	8.03	13.08	9.53	1.4

*QFM indicates quantitative carotid blood flow; CVD, cerebrovascular disease; H/L, high-low flow ratio; TIA, transient ischemic attach; INF, infarction; MIN, minimal (<25% stenosis); and ND, not done. In patients 1 through 19, results were true positive (angiogram, >70% stenosis; QFM flow ratio, >1.25); patients 20 through 23, false negative (angiogram, >70% stenosis; QFM flow ratio, <1.25); patients 24 through 62, true negative (angiogram, <70% stenosis; QFM flow ratio, <1.25); and patients 63 through 70, false positive (angiogram, <70% stenosis; QFM flow ratio, >1.25).

1.4 had significant carotid stenosis without any false-positive results (Table 3). We believe our data confirm that flow is not likely to vary significantly until hemodynamically significant stenosis occurs and, therefore, recommend that a flow ratio of greater than 1.4 be considered highly suggestive of significant carotid stenosis; a ratio of 1.3 to 1.4, indeterminate; and a ratio of less than 1.25, normal.

Unilateral atherosclerotic disease appears to be common (Table 4), with the contralateral vessel usually becoming the major collateral vessel. When both vessels have high-grade stenosis, the vessel with the lower-grade stenosis is usually dominant, as reflected in an abnormal high-low flow ratio. The absolute value for flow varies considerably in normal subjects and in nonstenotic arteries of patients with cerebrovascular disease (in this series, as low as 3.75 and as high as 11.54 mL/s for the latter group). Considering the absolute flow alone as a diagnostic criterion would result in falsely assuming a normal artery in cases with bilateral flow in the normal range with considerable side-to-side variation (see cases 4 and 12 through 14). Likewise, an abnormally low value can only be evaluated in the context of the contralateral side. For example, patients 19 and 38 had similar "abnormal" low flows of 3.75 and 4.14 mL/s; however, contralateral flows were markedly different, and the flow ratio was 2.7 for the patient with underlying significant carotid disease and 1.2 in the stenosis-negative case. Thus, although the QFM is useful in identifying and studying high-grade carotid stenosis, flow patterns, and collaterization, the flow ratio is most specific for significant carotid stenosis.

We have shown that the QFM detects significant carotid stenosis and reflects the collaterization pattern of elevated flow through the contralateral carotid circulation. An ipsilateral collateral pattern through external carotid branches or similar flow in the two common carotid arteries can result in a false-negative QFM study. Carotid QFM can be used to screen for carotid bifurcation stenosis, with an abnormal flow ratio highly predictive of significant carotid stenosis. In addition, the QFM can be used to assess further duplex-positive cases in which the spectrum is borderline for hemodynamically significant carotid disease. Further work is necessary to determine whether changes in stenosis and/or collateral flow can be detected over time.

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Variations in Dorsomedial Hand Innervation

Electrodiagnostic Implications

Alison Reichard Peterson, MD; Michael J. Giuliani, MD; Megan McHugh, REDT; Carol Christy Shipe, REDT

• Sensory potentials recorded from the dorsal cutaneous branch of the ulnar nerve (DCUN) help localize ulnar nerve lesions. This conduction technique was first described by Jabre in 1980. Abnormalities detected with this technique in control populations are commonly attributed to local trauma. Anatomic variations of cutaneous innervation to the dorsum of the hand, however, have been described. We recorded DCUN responses using both the normal DCUN stimulation point and a secondary site of stimulation at the radial aspect of the forearm in 44 patients. Eleven patients demonstrated a low-amplitude DCUN response. Four of the 11 patients demonstrated sensory potentials obtained from the routine recording site of the DCUN with radial stimulation. We conclude that an abnormal DCUN response may represent anomalous innervation. To avoid some errors in localization, radial forearm stimulation should be performed whenever the DCUN response is abnormal.

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After carpal tunnel syndrome, the most common focal nerve entrapments of the upper extremity involve the ulnar nerve. The majority of ulnar nerve entrapments occur at the elbow, while the second most common location is at the wrist. Unfortunately, clinical and electrophysiologic distinction between these proximal and distal lesions is often difficult.[1] The dorsal cutaneous branch of the ulnar nerve (DCUN) conduction study helps improve localization.

The DCUN is a pure sensory nerve that usually leaves the main trunk of the ulnar nerve 6 to 8 cm proximal to the ulnar styloid process. It supplies the dorsomedial aspect of the hand. At the branching point, the DCUN becomes subcutaneous and is more accessible to nerve conduction studies. A normal response supports the conclusion that the lesion is distal to the branching point of the DCUN.[2] Conversely, an abnormal DCUN response suggests a proximal lesion. However, the electrophysiologic distinction between distal and proximal lesions is not always clear-cut. Normal responses of specific individual sensory and/or motor potentials are possible in axon-loss lesions involving the ulnar nerve and may be recorded distal to the site of ulnar nerve injury. Selective involvement of individual fascicles at the site of injury is the proposed mechanism.[3] For this reason, the DCUN and other distally recorded responses may be normal in the setting of a proximal lesion if those particular fascicles are spared. Despite these limitations, in conjunction with both clinical and other electrophysiologic information, the DCUN technique is useful.

Although the DCUN conduction study is widely used, anomalous innervation patterns involving the sensory distribution of the dorsomedial aspect of the hand are rarely described in electrophysiologic terms. Anatomic work has demonstrated variability in the cutaneous innervation of the dorsal surface of the hand.[4,5] The DCUN may arise from the ulnar trunk at the elbow[5] or may be entirely absent.[4] When absent, the superficial radial nerve (SRN) may supply the entire dorsum of the hand. There are also rare reports of dorsomedial hand innervation by the musculocutaneous or posterior cutaneous nerve of the forearm.[5] The limited electrophysiologic studies addressing the innervation pattern to the dorsum of the hand and its variability provide few clear guidelines concerning the frequency or methods to deal with this variability. Kim et al[2] recommend radial stimulation of the DCUN if it is difficult to obtain a response using the routine site of stimulation but provide no further details.[2] Hoffman et al[6] suggest that an abnormal response may indicate DCUN injury. Jabre[7] noted that 11% of the subjects in his series had an asymmetric DCUN amplitude response with at least 50% difference between sides, which he attributed to a local nerve lesion. In the best study concerning the normal variability of the cutaneous innervation to the dorsum of the hand, Spindler and Felsenthal[8] evaluated SRN conduction in the hand. They concluded that 65% of 30 control subjects had only radial innervation extending to the third web space on nerve conduction studies. Seventy-three percent had only a DCUN response to the third web space, 40% had dual innervation, and none had a radial response at the fourth web space, which is usually innervated by the DCUN.[8] The findings of Spindler and Felsenthal, therefore, conflict with previous anatomic descriptions of the sensory innervation to the dorsum of the hand.[4,5]

To reconcile the difference between this electrophysiologic study and previous anatomic reports, 51 patients underwent nerve conduction studies to determine whether the DCUN distribution is ever supplied by the radial nerve.

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This has important clinical implications for any laboratory utilizing the DCUN study for localization of ulnar nerve lesions.

PATIENTS AND METHODS

A total of 102 limbs of 51 patients (10 men and 41 women) were studied. The patients' ages ranged from 20 to 81 years (mean, 40.2 years). Seven patients had abnormal results of routine ulnar and/or radial nerve studies. These patients were excluded to eliminate the possibility of confounding variables of radial or ulnar nerve disease. Forty-four patients were therefore analyzed in our study.

All patients underwent radial, median, and ulnar sensory studies. In addition, median and ulnar motor studies were performed. Antidromic stimulation was used for all sensory studies. Limb temperature was recorded from the dorsum of the hand and was maintained at 32°C. For the DCUN study, a plastic mounted bipolar electrode with a 3-cm interelectrode distance (electrostatic shielding by Medmark, Yucca Valley, Calif) was placed on the dorsum of the hand between the fourth and fifth metacarpal bones (ie, fourth web space), slightly distal to the resulting anatomic "V." The reference electrode was placed distally. The ground was placed between the stimulating and recording electrodes. The cathode of a bipolar felt-tipped stimulator (TECA Corp, Pleasantville, NY) was placed approximately 8 to 10 cm proximal to the active electrode, wherever the best response was obtained between the flexor carpi ulnaris tendon and the ulna. The anode was placed proximally. With the same electrode recording setup, the stimulator was moved to the radial side of the forearm at the same level as the previous stimulation for the routine DCUN study (Fig 1). Using the setup described above, we added recording sites from the first through the third web spaces in patient 4. Four recordings were obtained simultaneously from the first through the fourth web spaces with the radial and ulnar stimulation sites described above. Bipolar electrodes (described above) were used for all recordings.

All patients underwent DCUN testing of both upper extremities. An electromyograph (Dantec Neuromatic 2000, Dantec Electronics Inc, Allendale, NJ) was used to measure all potentials. Filter settings for the sensory responses were 20 Hz and 2.0 kHz. Stimulus duration was 0.2 milliseconds. Latencies were measured from stimulus onset to takeoff from baseline and to the first negative peak. Conduction velocities were calculated with use of the takeoff from baseline latency. Amplitudes were measured from baseline to the negative peak. We used reference age-related indexes (ie, age-adjusted norms), which were obtained by pooling data from healthy individuals that were categorized by decade. A sensory nerve action potential was also considered abnormal if there was a 50% or greater difference between sides, despite a normal absolute amplitude.

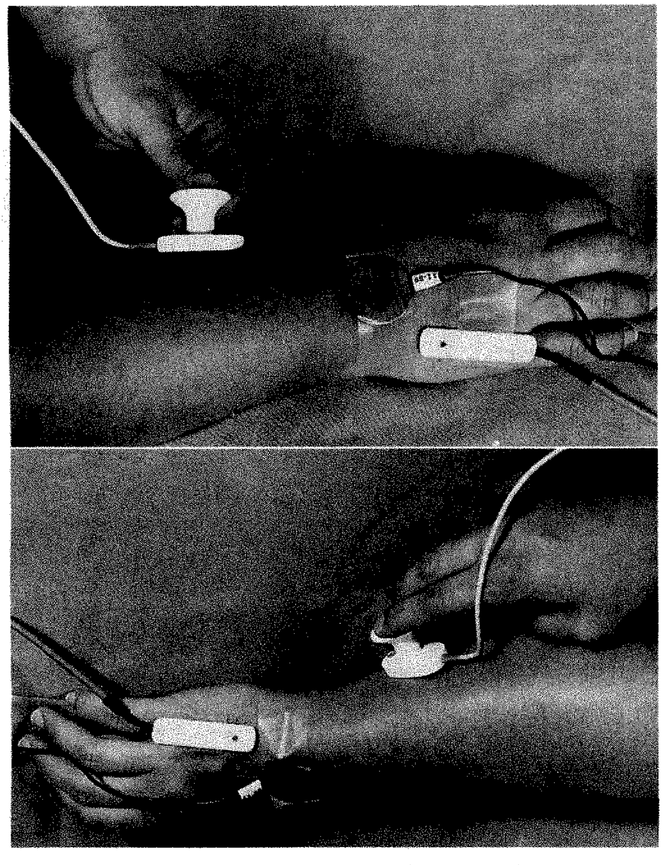

Fig 1.—*Placement of stimulating and recording electrodes for dorsomedial sensory recordings for radial (top) and dorsal cutaneous ulnar (bottom) nerves.*

RESULTS

Eleven patients (24%) had a low-amplitude DCUN response (Table 1), and five patients had a radial stimulated response (RSR) while recording from the dorsomedial aspect of the hand. Two patients (patients 1 and 2, Table 2) had a low-amplitude DCUN response bilaterally, with at least a single RSR. Patient 1 had a unilateral RSR. The amplitude was equal to the DCUN response on the same side, while the opposite hand had a low-amplitude DCUN response without an RSR. Patient 2 had bilateral RSRs. The DCUN response was absent on the right side and had a low amplitude on the left side. The amplitude of the left-sided RSR response was approximately 50% that of the DCUN amplitude on the same side. Both RSR responses were symmetrical in amplitude. Two patients (patients 3 and 4, Table 2) had a unilateral low-amplitude DCUN response and an ipsilateral RSR. The amplitude of the RSR of patient 3 was 33% that of the DCUN response on the same side. Patient 4 had a unilateral RSR and an absent DCUN response on the same side. The innervation of the dorsal aspect of this patient's hand appeared to be entirely radial, as illustrated with four simultaneous recordings (Fig 2). The remaining patients had a low-amplitude DCUN response (three bilateral and four unilateral) and no RSR.

Of 33 patients with normal DCUN responses, only one showed an RSR on the left (patient 5, Table 2). This response was 9% that of the DCUN response and was of a relatively smaller amplitude compared with the patients with RSRs and abnormal DCUN responses.

Patients with RSRs ranged in age from 20 to 55 years (mean, 36.8 years). The RSRs ranged in amplitude from 3.0 to 10.4 μV (mean, 6.7 μV), and the latencies ranged from

Table 1.—Summary of Low-Amplitude DCUN Responses*

	Abnormal DCUN Responses	Unilateral RSR	Bilateral RSR	Total (%) With RSR	Total (%) Without RSR
No. of patients	11	3	1	4/11 (36.4)	7/11 (63.6)

*DCUN indicates dorsal cutaneous branch of the ulnar nerve; RSR, radial stimulated response recorded from the dorsomedial aspect of the hand.

2.0 to 3.5 milliseconds (mean, 2.5 milliseconds). The RSR nerve conduction velocities were normal, ranging from 50 to 67.9 m/s (mean, 58.0 m/s).

COMMENT

Twenty-five percent of the limbs in our series had a low-amplitude or absent DCUN response. Patients' occupations included clerical, technical, student, and waitress. Hobby interests were also explored and were similar to the occupational histories in that they revealed no predisposition to repetitive trauma. Also, one of our patients had a normal DCUN response with partial innervation by the SRN, arguing against trauma as the cause of cutaneous sensory redistribution. In addition, 36.4% of these limbs demonstrated anomalous innervation to the dorsomedial aspect of the hand from the radial nerve. Therefore, we conclude that local trauma does not explain the abnormalities of an isolated DCUN response in all patients, as sug-

Table 2.—DCUN and RSR Amplitudes and Conduction Velocities in Patients With Anomalous DCUN Innervation*

	DCUN					RSR			
	Amplitude, µV			Conduction Velocity, ms		Amplitude, µV		Conduction Velocity, ms	
Patient No.	Right	Left	Age-Adjusted Norms	Right	Left	Right	Left	Right	Left
1	10.0	10.4	>12	52.6	53.1	NR	10.4	NR	50.0
2	NR	15.0	>18	NR	50.0	7.0	7.2	56.0	56.0
3	30.0	15.2†	>12	66.7	77.3	NR	5.2	NR	59.4
4	NR	20.0	>18	NR	61.5	8.4	NR	58.8	NR
5‡	32.0	20.0	>10	61.5	61.5	NR	3.0	NR	67.9

*DCUN indicates dorsal cutaneous branch of the ulnar nerve; RSR, radial stimulated response recorded from the dorsomedial aspect of the hand; and NR, no response.

†Value is abnormal because of 50% asymmetry.

‡Patient 5 was the only patient with a normal DCUN response and an RSR.

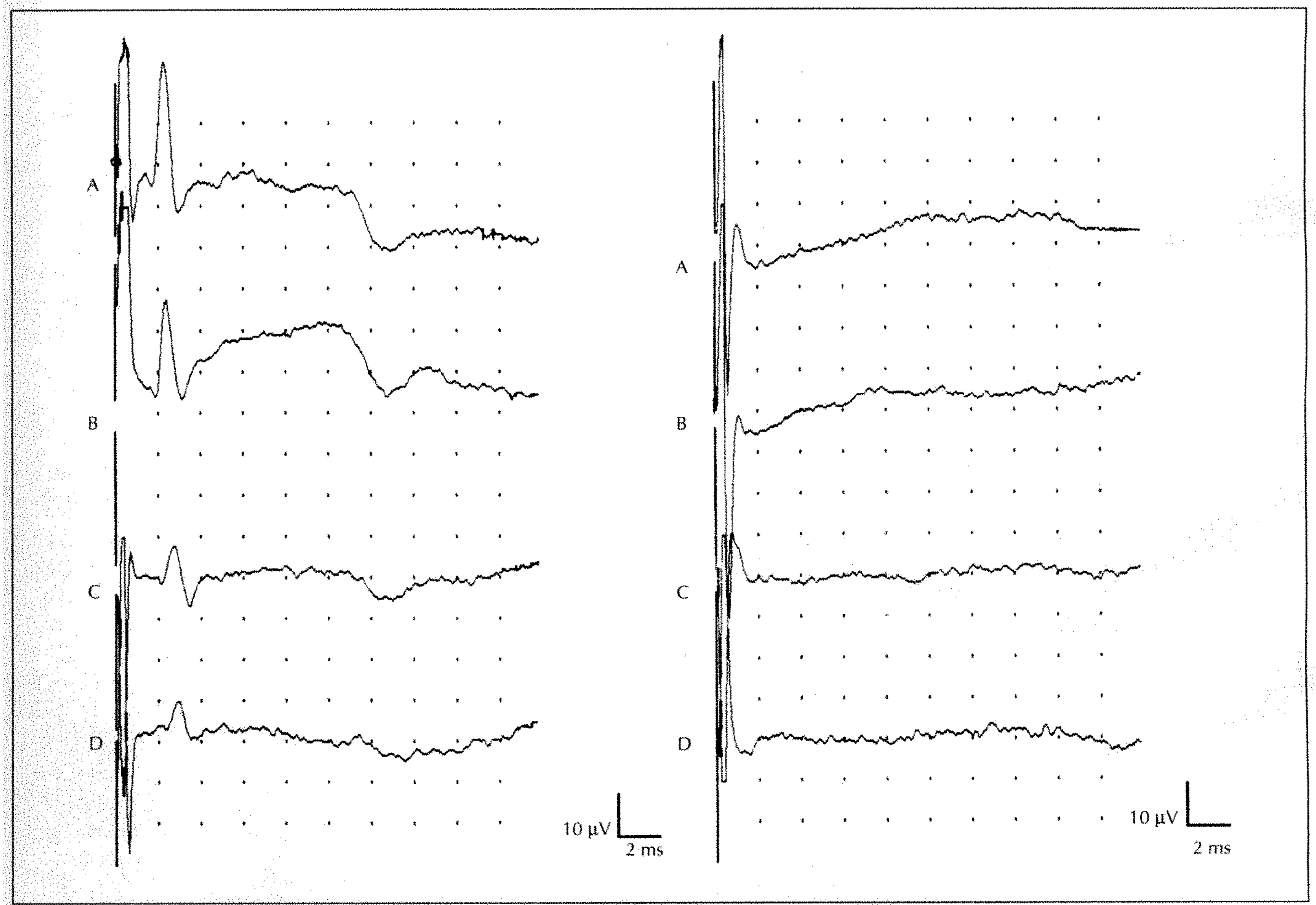

Fig 2.—*Right-handed dorsomedial sensory recordings from patient 4 with radial (top) and dorsal cutaneous ulnar (bottom) stimulation while recording from the first (A), second (B), third (C), and fourth (D) web spaces.*

gested in previous reports.[6,7]

Our results differ from those of Spindler and Felsenthal,[8] who found no RSR responses on the dorsomedial aspect of the hand. One reason they may not have found RSR responses is the low incidence of this finding and their small sample size. A second reason for the difference between our findings and those of Spindler and Felsenthal could be related to technique. The stimulation site for the RSR has no clear-cut anatomic landmarks. The SRN divides into lateral and medial branches. The lateral branch supplies the thumb. The medial branch divides further into four branches, supplying the dorsum of the second, third, and fourth digits.[8] The stimulation site used by Spindler and Felsenthal was distal to that used by us. Therefore, it is possible that they were stimulating a site distal to the branching point of the most medial branch of the medial division of the SRN, which supplies the ulnar aspect of the hand. Commonly, these divisions branch slightly above the wrist[9]; however, variations of this pattern may occur. A third difference between their report and ours is that they always found a DCUN response. Two of our patients had an absent DCUN response on one side. Kim et al[2] refer to difficulty obtaining a response and recommend the techniques of radial stimulation in the setting that we used. We cannot reconcile why we along with Jabre[7] and Kim et al[2] had difficulty obtaining a DCUN response in all patients, while Spindler and Felsenthal did not. However, our findings are supported by anatomic studies demonstrating SRN innervation to the dorsomedial aspect of the hand.[5]

Because ulnar mononeuropathies are frequently referred to the electromyography laboratory and localization is often difficult,[1,3,10,11] our findings are important. A low-amplitude DCUN response is used to localize ulnar mononeuropathies. Our findings suggest that an absent, asymmetrical, or low-amplitude DCUN response may be due to exclusive or partial SRN innervation. Therefore, we recommend that in the presence of a low-amplitude DCUN response, radial forearm stimulation should be performed to identify anomalous innervation.

We wish to thank Michael J. Painter, MD, for his review of the manuscript.

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CORRECTION

Figure Legends Misplaced

In the article titled "Cerebral Blood Flow Deficits in Hereditary Essential Myoclonus," published in the February issue of the ARCHIVES (1992;49:179-182), on page 180 figure legends 2 and 3 were transposed.

The Pathogenesis of Tourette's Syndrome

A Possible Role for Hormonal and Excitatory Neurotransmitter Influences in Brain Development

Roger Kurlan, MD

• Tourette's syndrome (TS) is associated with prominent gender differences in clinical expression, tics with a sexual content, and a stabilization or improvement of symptoms after puberty. It is herein hypothesized that some tics can be viewed as inappropriately expressed (normally inhibited) fragments of primitive motor and vocal programs involved in reproductive activity. The brain regions involved in TS (basal ganglia and limbic system) are proposed to be counterparts in humans of those functioning in primitive reproductive behavior whose development and organization are under sex hormome control. It is further hypothesized that sex hormone action is mediated by excitatory neurotransmitter mechanisms such that an excessive trophic effect occurs early in development and a neurotoxic environment emerges later on. The defective gene in TS is hypothesized to influence these developmental processes. This hypothesis has implications for the investigation of the pathogenesis of TS and for experimental therapeutics of the disorder.

(*Arch Neurol.* 1992;49:874-876)

Tourette's syndrome (TS) is a childhood-onset disorder characterized by the presence of motor and vocal tics and specific behavioral dysfunction, including obsessive-compulsive disorder.[1] Clinical and epidemiologic studies indicate that TS is hereditary, but its pathogenesis remains unknown. Previously published hypotheses regarding the pathogenesis of TS have implicated increased central dopaminergic transmission and possible disturbances of other neurotransmitter systems.[2] Devinsky,[3] who recognized a similarity between tics, vocalizations, and obsessive-compulsive symptoms of patients with encephalitis lethargica and TS, postulated that TS is the result of dopaminergic dysfunction arising from disturbances in the midbrain.

Herein, I offer a hypothesis based on the distinctive clinical features of TS and the recently elucidated basic neurobiologic mechanisms underlying normal brain development. I suggest that TS is due to abnormal development of specific components of the basal ganglia and limbic system. The systems involved are those subserving primitive, vestigial reproductive functions, and the normal maturation and maintenance of these systems, I propose, are under sex hormone control, which in turn is mediated by excitatory amino acid (EAA) neurotransmitter mechanisms. I hypothesize that TS may result from a disturbance in one or both of these hormonal and neurochemical control processes.

CLINICAL EVIDENCE FOR SEX HORMONE INFLUENCES

For perhaps no other neurologic condition is the gender difference in clinical expression so remarkable as in TS. Tourette's syndrome occurs with a striking male predominance, with a male-to-female ratio of approximately 3:1.[2(pp65-74)] Segregation analysis of families affected by TS suggests autosomal dominant inheritance with gender-specific penetrances and expression.[4] For males, penetrance is nearly complete when only tics are considered. For females, penetrance estimates rise from 56% when only tics are considered to 70% when obsessive-compulsive disorder is included as an alternative expression of the putative TS gene. Thus, particularly in females, obsessive-compulsive disorder appears to be a variant in the clinical expression of the TS genetic defect. Associated attention deficit hyperactivity disorder is more common in male patients.[2(pp65-74)]

The natural history of TS suggests a developmental disturbance that is influenced by sex hormone status. The usual onset of TS in the first decade of life is indicative of a developmental disorder. A major milestone in the natural course of TS occurs near the time of puberty, a time of major changes in sex hormone secretion, after which most affected individuals show a stabilization of symptoms and subsequent improvement or resolution.[5] Clinical reports have indicated that alterations in sex hormone levels, including menarche, menstrual cycle, use of oral contraceptives and androgenic steroids, menopause, and pregnancy, may affect the symptoms of TS.[2(p187),6] With these observations, it has been suggested that the gene for TS is under sex hormone control.[6] I now suggest that posttranscriptional processes related to the development of specific brain regions represent alternative sites for the action of sex hormones in TS.

SEX HORMONE CONTROL OF BRAIN DEVELOPMENT

It is now recognized that gonadal steroid hormones play an important role in the structural organization of neural pathways involved in reproductive function.[7] Sex steroids determine the composition and synaptic relations of neural circuits not only in early development but also in later life stages. The lifelong organizational effects of sex hormones include the determination of the relative numbers of neurons devoted to specific functions, an influence on the synaptic relationship between steroid-sensitive neurons and their targets, and the organization of the afferent input to steroid-sensitive neurons.

For example, it is known that androgens regulate the neuronal number and the efferent and afferent connections

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of motor neurons in lumbar segments of the rat spinal cord that innervate striated muscles attached to the penis.[7] In this model, the size, numbers, and connections of the spinal motor neurons differ significantly between male and female animals. In certain songbirds, a courtship or territorial song is produced exclusively by males, and the brain regions controlling song exhibit the most robust sex differences in neuronal number described to date in the vertebrate central nervous system.[8] In the zebra finch species, between 20 and 90 days after hatching, female birds (which do not sing) lose neurons in the lateral magnocellular nucleus of the anterior neostriatum, a forebrain region specifically implicated in song learning[8]; these neurons are normally retained in the male birds of the species. Neuronal loss can be prevented in female birds if they are exposed to estrogen before day 20 after hatching, a treatment that also instills the capacity for male-typical song.[9]

There is also evidence that sex steroids may play a role in the formation of major projections of neurons in the song system.[7] Similar sex differences in neuron numbers have been identified in a variety of species and tissues, including hypothalamus, superior cervical, and hypogastric ganglia of rodents, frog vocal control systems, cat sympathetic preganglionic neurons, and dog and human spinal cord.[7] In many instances, sex hormones are responsible for these gender differences. Evidence for hormonal control of neuronal projections and synaptic connections in several model systems has also been presented.[7]

I propose that brain regions involved in TS are counterparts in humans of those regions functioning in primitive reproductive behavior whose development and organization are under sex hormone control. A variety of programmed motor behaviors (eg, mating "dances," sexual foreplay, and mounting behavior) are characteristic of reproductive activities for many animal species. Vestiges of such motor programs may be located in the basal ganglia, part of the most phylogenically ancient components of mammalian brains, and expressed inappropriately in TS as sexually related complex motor tics, such as touching, rubbing, licking, sucking, kissing, smelling, pelvic thrusting, and copropraxia (obscene gestures, such as masturbatory movements). Also involved may be regions subserving vestigial vocal components of reproductive behavior (eg, mating songs and noises) and manifested in TS by a range of sexually related simple (eg, sniff, grunt, bark, and pant) and complex vocal tics. This proposition might explain why verbalization with a sexual content (ie, coprolalia) is a characteristic and cross-cultural component of the TS vocal repertoire. In this conceptualization, certain tics can be viewed as inappropriately expressed (ie, normally inhibited) fragments of primitive motor and vocal programs involved in reproductive activity.

Lesioning and electrical stimulation studies in fishes, amphibians, reptiles, birds, and mammals suggest that certain mating and courtship functions may reside within the basal ganglia and homologous regions.[10] The occurrence of inappropriate sexual behavior, such as exhibitionism, in association with TS supports the notion that brain regions involved in reproductive behavior are disturbed in TS.[11]

Studies have shown that the cytoarchitecture of the striatum undergoes considerable transformation to achieve its characteristic adult form.[12] Components in this process that might be affected in TS are the so-called dopamine islands, striosomal structures that are key foci in the early development of the striatum. Dopamine islands are the sites of early, concentrated synaptogenesis in the striatum and are important in the development of neuronal projections to substantia nigra.[12]

Limbic systems, associated with motivational and emotional aspects of reproduction, may also be involved in TS. Dysfunction of limbic regions has been implicated in the pathogenesis of obsessive-compulsive and other features of TS.[13] Sex differences in neuronal morphologic features have been described in the squirrel monkey amygdala,[14] but other limbic regions and the basal ganglia have received little investigative attention in this regard. Sex differences in the function of the extrapyramidal system have been observed in a variety of investigations,[15,16] and a cell culture study has suggested that mesostriatal and mesolimbic dopaminergic systems assume an early role in the development of some sexual dimorphisms in the brain.[17]

THE ROLE OF EAA SYSTEMS

Excitatory amino acid pathways are abundant in the brain, estimated to be the primary neurotransmitter in approximately 50% of the synapses in the mammalian forebrain. Major EAA pathways involve the basal ganglia and limbic regions. Recent work indicates that EAAs possess important neurotrophic influences, participate in the development of neuronal circuitry and cytoarchitecture, and regulate activity-dependent synaptic plasticity during development. Excitatory amino acids released from nerve terminals appear to have trophic properties during brain development.[18] Exogenously applied *N*-methyl-D-aspartate, for example, promotes cell survival in cerebellar granule cell cultures in a dose-dependent manner.[19] *N*-methyl-D-aspartate has also been demonstrated to enhance neuronal survival in dissociated spinal cord cultures.[20] L-glutamate also has trophic properties.[18] In addition to promoting neuronal survival, EAAs regulate axonal neurite outgrowth and modulate dendritic growth in some neurons.[18] The synaptic mechanisms of EAA neurotransmission are important during development for selection and stabilization of appropriate neuronal circuitry, such as occurs as part of learning and memory as well as experience-dependent plasticity of the visual pathways.[18]

In contrast to these promotional functions in brain development, excessive activation of EAA receptors can initiate a series of intracellular biochemical events that cause neuronal damage, a process referred to as "excitotoxicity." Excitotoxic mechanisms have been implicated in the pathogenesis of degenerative (eg, Huntington's disease and cerebellar degeneration) and other neurologic (eg, hypoxic-ischemic injury and epilepsy) disorders.[21]

Of relevance to the pathogenesis of TS, the sensitivity of neurons to EAA neurotoxicity changes markedly during development. Different brain regions and different neuronal types exhibit their own developmental profile of susceptibility to a variety of selective EAA receptor agonists.[18] For example, although kainate is a potent neurotoxin in the adult brain, it is relatively nontoxic in the immature brain.[22] Thus, it is possible that EAA influences in identical brain regions may be trophic in an early stage of development and toxic at a later time or in the setting of genetically programmed or acquired diseases. Recent evidence indicates that sex hormone influences on neuronal populations subserving song in certain bird species may be mediated via alterations in surface *N*-methyl-D-aspartate receptors. Thus, under the influence of androgens, song-related neostriatal neurons in males have reduced *N*-methyl-

D-aspartate binding compared with those in females, a finding that may explain why they are spared from programmed excitotoxin-mediated cell death (Earnest J. Nordeen, PhD, written communication, November 1991). It is possible that other mechanisms, such as neural trophic factors, may be involved in the regulation of brain development by sex hormones.

HYPOTHESIS

Based on the above considerations, I offer the following hypothesis regarding the pathogenesis of TS. The defective gene(s) of TS is one that influences the developmental processes for basal ganglia and limbic regions that subserve (in a vestigial fashion) primitive motor, vocal, and emotional processes involved in reproductive behavior. Under the influence of gonadal steroid hormones, there is disordered development, and an abnormal number or circuitry of neurons is established. The sex hormone influence is mediated by EAA mechanisms, such that an excessive trophic effect occurs early in development, resulting in an inappropriately increased neuronal number and/or excessive neuronal process outgrowth.

In support of this hypothesis, Balthazar[2(p254)] found an increase in the number of small neurons in the caudate nucleus and putamen in the postmortem brain of an adult patient with TS. Because of the similarity of that brain, histologically, to a normal brain early in development, the author suggested that TS might be caused by a developmental arrest or anomaly of the striatum. Furthermore, Singer and colleagues[23] recently studied the postmortem striatum from three adults with TS and found a significant increase in neuronal dopamine uptake carrier sites, as measured by tritiated mazindol binding, indicating excessive dopamine innervation within the striatum.

I further hypothesize that, over time and particularly near the time of puberty under the influence of sex hormones, EAA-mediated mechanisms result in an excitotoxic environment with resultant normalization of previously excessive neuronal numbers, processes, or both. This scenario would explain the tendency of TS to improve or resolve after adolescence. It also predicts that patients with TS might show signs of basal ganglia and/or limbic degeneration late in life. Several genes have now been identified that participate in both neuronal development and programmed death in vertebrates and invertebrates.[24,25]

IMPLICATIONS OF THE HYPOTHESIS

While dopamine, serotonin, acetylcholine, opioid, and other neurotransmitter systems have been studied in relationship to the pathogenesis of TS, little attention has been focused on EAA functions. Postmortem studies of EAA receptor binding may prove valuable, particularly if careful attention is paid to temporal relationships. Thus, under the hypothesis presented herein, binding patterns for EAA receptors may differ significantly in the brains of 5-year-old and 40-year-old patients with TS. Investigations directed at clarifying the relationship between sex hormone influences on brain development and EAA mechanisms may prove enlightening. The hypothesis predicts that a sex hormone influence on the normal development of some basal ganglia and limbic regions will be identified. Furthermore, the hypothesis provides a framework for developing experimental therapeutic interventions in TS, particularly through manipulations of hormonal and EAA systems. Under the hypothesis, it is proposed that male sex hormones have an adverse effect and female hormones a beneficial effect on disordered brain development in TS. Studies are under way, for example, to assess the effects of flutamide, an antiandrogenic agent, on the symptoms of TS (Bradley S. Peterson, MD, oral and written communication, April 1992).[26] If current genetic linkage analysis studies in TS prove successful, a population of gene-carrying, presymptomatic individuals will be identified, providing for early, neuroprotective therapies designed to ameliorate or correct abnormalities of brain development.

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Cost-Containment and the Practice of Neurology

The Conflict of Canons

Matthew Menken, MD

During the past 25 years, dramatic changes in the practice of neurology have been nourished by major advances in basic and clinical neuroscience research, and the development of new technology. At the same time, it is difficult not to be concerned that the practice of neurology (and medicine generally) appears to be changing from a professional activity into a business.[1] This is surprising, because medical practice has always reflected a blend of financial self-interest on the one hand, and the eleemosynary and solicitous characteristics of a profession on the other. However, professional obligations have traditionally outweighed business interests, collegial rather than competitive relationships with peers predominated, the ability to earn an adequate income in virtually any field of practice was assumed by medical students and residents (and so was rarely given much attention), and the intraprofessional status and prestige of the several specialties and subspecialties tended to be independent of the mean earnings of its members. Furthermore, most practitioners and organized medicine insisted that all physicians' earned income derive from individual effort (personal or personally supervised care), without promotional advertising, marketing gimmicks, or the capitalist ventures of entrepreneurs.

Several factors have probably contributed to a more commercial climate of practice recently, and a heightened awareness among residents and practitioners of the business aspects of medical care. First, a greatly expanded supply of physicians promotes rivalry for patients with private insurance and turf battles among the specialties. Second, a corps of administrative personnel attempts to lower the cost of care by micromanagement of our clinical decisions. This oversight increases practice (and administrative) costs, in part through redundant paperwork including authorization requirements. Third, a litigious environment of practice encourages "defensive" medical demeanor and the pessimistic viewpoint that patients are potential adversaries. Finally, the tendency of the judicial system to view medical practices as business firms subject to antitrust regulation protects physicians from peer pressure (and peer censorship) when they advertise in the lay press and media, or participate in entrepreneurial ventures.[2]

In my view, the introduction of Medicare 25 years ago has also been a critical step in the development of a business orientation for medical and neurologic practice. This is a contradiction, since this social legislation unquestionably provided access to needed care for many older and disabled Americans. However, when compared with the public insurance and vertically integrated health care financing of other nations, such as the British National Health Service (NHS), this limited intrusion of the US government into the health marketplace has proved to be far more inflationary. By preserving until recently such attributes as a per diem reimbursement system for hospitals, and a largely self-determined fee-for-service payment system for physicians, the vastly increased flow of funds into the health system generated by Medicare created accelerating inflation in the pricing of health services that has yet to be controlled.[3] For example, spending under Medicare part B (mostly physicians' services) increased from \$280 to \$1072 per enrollee in a single decade ending in 1988, or 283%. Thus, it is not surprising that the 1980s were characterized by a growing consensus among the public and its elected officials that something must be done to curtail the costs of the Medicare program.

In this context, it is noteworthy that so much attention has been given in recent years to the effects of physician behavior and the operating characteristics of hospitals on the economics of medical care, and yet so little attention has been paid to the reciprocal effects of cost-containment policy on the fundamental moral fabric of medical care. This is an appropriate time for neurologists to examine these issues, since an entirely new Medicare framework for payments to physicians is being phased in between 1992 and 1996, without important questions having been answered concerning the potential for good economics to harm good neurologic care. Recent history suggests that when the canons of economics assume a normative value, other goals may be sacrificed in the process. For example, since the Medicare diagnosis-related group prospective payment system for hospitals was introduced as a cost-containment device in 1983, many voluntary hospitals have adopted characteristics usually associated

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with for-profit hospitals, such as ownership of for-profit businesses, aggressive advertising, and the recruitment of administrators trained as corporate executives, with little time or motivation to preserve the charitable nature and healing function of hospitals that anchor these institutions to the public interest.[4]

MEDICARE PHYSICIAN PAYMENT REFORM

In 1986, Congress created the Physician Payment Review Commission to advise it on appropriate ways to reform the system of compensation of physicians. This followed from the perception that rapidly rising payments to physicians created a hardship for taxpayers as well as the 33 million elderly and disabled beneficiaries. There was also a growing awareness that the system of paying physicians on the basis of historical charges rewarded physicians for the performance of procedures and operations much more than for evaluation and management (cognitive) services, thus distorting the optimum mix of services provided to patients through inappropriate financial incentives.

In the Omnibus Budget Reconciliation Act of 1989 a new system of physician payment based on resource costs was introduced—the resource-based relative value scale.[5] In this scale, resources include equipment, supplies, and "human capital." The objective of the resource-based relative value scale framework is to determine those relative prices that would exist in a competitive market, on the theory that such prices promote the optimum use of scarce health care resources relative to patient needs and demands. The relative value of each service is based on the work (time and effort) involved, practice costs, and the cost of malpractice insurance. Payment for a service is determined by multiplying the relative value of each service by an arbitrary dollar-based conversion factor. A geographic adjustment factor takes into account regional differences in practice expenses and (partially) adjusts for differences in the cost of living.[6]

The new fee schedule is to be phased in over 5 years (1992 to 1996), with about 40% of the changes implemented in the first year. In addition to a new fee schedule, the legislation also prohibits charges to patients above fee schedule limits (balance billing), and expands federal funding for effectiveness research and the development of practice guidelines. This new physician payment framework initially received the support of national organizations that represent primary care and other physicians and by the American Medical Association, which believed it preferable to other proposals to base physicians' payments on capitation rates or diagnosis-related groups. More recently, professional support has nearly vanished as many physicians, the Physician Payment Review Commission, and the American Medical Association "feel betrayed" by the actions taken by the Health Care Financing Administration in developing the rules to implement the legislation.[7] Although Congress writes Medicare legislation, the executive branch, which is committed to a reduction in the federal budget deficit without additional taxes, generates the regulations; the Health Care Financing Administration rules are subject to the approval of the Department of Health and Human Services and the President's Office of Management and Budget.

Perhaps the most controversial aspect of the new legislation is the linkage established between the volume of services provided by physicians and payments to physicians, by means of a volume performance standard. For example, in June 1991, the Health Care Financing Administration proposed an implementation plan, which assumes that Medicare expenditures will increase 50 cents for every $1 reduction in physician payments due to an increase in the volume of services provided by physicians as a means of maintaining their previous levels of income—the behavioral offset.[8] Under the volume performance standard, if total Medicare payments to physicians in a given time period exceed a projected amount, fees will subsequently be reduced to compensate for the surplus. The stated objective is to increase the appropriateness of care by providing incentives for all physicians to become involved in the process of allocation of resources. The implicit supposition is that physicians usually have sufficient information to reach a consensus concerning the appropriate and inappropriate use of many frequently performed and expensive procedures and surgical interventions.

Put summarily, physicians' fees under Medicare will henceforth be determined by government-administered prices, without a mechanism for direct negotiations with medical associations (as in Canada and Western Europe), a process that has been called *social arbitration*.[9] The decision to fix fees unilaterally by the central government is noteworthy, given the stated administration philosophy of allowing markets to allocate resources to the greatest extent possible. Clearly, the Congress, Physician Payment Review Commission, and Health Care Financing Administration, are all moving in the direction of an annual predetermined global budget for all physicians' services, although this has yet to become a stated objective.

CAN COST-CONTAINMENT GO TOO FAR?

In recent years, the economics of medical care seems to have acquired some of the characteristics of an ideology. The correction of economic pathology is all too often accepted uncritically, by professionals and the polity alike, as a self-justifying step.[10] To be sure, the economy and efficiency of medical and neurologic care are, or should be, a matter of great concern for all physicians. Annual health care expenditures of more than $600 billion more than justify detailed scrutiny of the organization of care and the allocation and use of resources. On the other hand, there is little doubt that the process by means of which physicians, hospitals, and other providers are paid or reimbursed can alter for better or worse the goals and objectives of health care—even though economics as an academic discipline lacks the capacity to reach normative conclusions about those values that should be incorporated into the health system. For example, when physicians in an ambulatory care center were awarded bonuses (in addition to salary) proportional to the gross monthly charges they generated, laboratory tests performed per patient visit increased by 23%, and x-ray films per visit increased by 16%, compared with the prior practice behavior of these physicians when paid by salary alone.[11]

Regardless of whether cost-containment is sought through regulation, marketplace competition, or both, there are only three ways that health care costs can be reduced.[12] First, the efficiency of health care delivery can be improved, that is, the system can provide the same total number of services with fewer real resources (hospital beds, physicians, medications). Second, the prices paid for these real resources can be lowered, that is, hospital reimbursements, physicians' fees, drug company profits, and so forth, can be trimmed. Third, the health system can deliver fewer services. Although the health system in the United States is exploring all of these approaches, there is little doubt but that the greatest reduction in total costs can be achieved by delivering fewer services—the "best" way.[12] For example, physicians' net incomes account for only 10% of all health care spending; therefore, a reduction of 20% in these incomes would reduce total health care spending only 2%.

In my view, the moral fabric of medical and neurologic care may be threatened by unbridled cost-containment. There is no scientific, objective, value-neutral manner by means of which to realize the trade-offs among accessibility, affordability, equity, and quality that are inevitably necessary in all modern health systems. These are fundamental moral questions of public policy as to the ends and purposes of health care that must be faced explicitly.[10] The public debate should be carried out in a more considered manner that makes clear the consequences of priority shifting, compromises, and the restriction of personal choice. Is there any doubt that such well-intentioned measures as price controls, expenditure caps, drug substitutions, and utilization ceilings, among others, have the potential to clash with the traditional moral function of neurologic medicine and the ideals of health care institutions where neurologists practice? For example, in a climate of government imposed cost-containment, can patients always assume that the neurologist will subordinate political dominion when that conflicts with what both parties in the physician-patient relationship believe to be in the best interest of the patient?

ILLUMINATING THE PROFESSIONALISM OF NEUROLOGISTS

If cost-containment has the dormant power to come into conflict with the well-being of the patient, then it is essential that physicians have sufficient public support to be heeded when we indicate those situations where economic factors should take second place. However, if we are to retain the credibility to defend the traditional values that define the healing process against competing social forces, then we must also be willing to subordinate self-serving interests when they conflict with the explicit commitments that demarcate professionalism—inclusive of those ambiguous situations where many fair-minded people perceive a dominance of vested interests, yet we do not.

Laws and rules may be expected to protect the public from impropriety and malfeasance, but do not render us immune from lucrative entrepreneurial incentives. Perhaps it is time to exorcise the spirit of Adam Smith from the field of neurology. Given the advances in medical and neurologic care and the explosion of technology since World War II, together with robust evidence of widespread practice variations, disciplinary differences in the norms of care, and the spreading commercialization of the health system, it is ever more enigmatic to assume with *The Wealth of Nations* (1776) that each specialty can seek individually determined goals and gains, yet be led by an "invisible hand" to promote the public interest. Our present dilemma in the medical commons is not conceptually unlike that of herdsmen who share a common pasture, all believing in the freedom of the individual to use the commons as each sees fit, and who are thereby ruined.[13]

Although the ethics of many types of entrepreneurial behavior by physicians has been debated extensively, none has received more attention recently than the issue of physicians' self-referrals. It is known, for example, that office-based physicians who perform their own imaging examinations (self-referrals) carry out lumbar spine radiography for patients with
low back pain 4.5 times more c
than nonperforming physicians
refer patients to other physician
lumbar radiography, and charg
average of 11% more for imagin
aminations of similar comple
While there is certainly the broa
possible divergence of opinion ir
matter of self-referrals, it is clear
the 1980s witnessed a steady incr
in the number of neurologists en
ing in entrepreneurial arrangem
involving self-referrals.[15] For e
ple, between 1984 and 1991 the n
ber of magnetic resonance ima
machines in Atlanta, Ga, incre
from 1 to 30, or more than twice
total number of magnetic reson
imaging scanners (12) in all of
provinces of Canada. Of the cur
number, seven are owned by pl
cians, six are owned by other e
preneurs, and 17 are owned by
pitals. In Florida, it has
estimated that one third of all pl
cians are investors in a variet
health care businesses.[16]

It is not surprising that the e
question of physicians' entrepren
ial activities has recently been
jected to close scrutiny by the
gress and is widely discussed ir
lay press. Unfortunately, the i
ence of neurologists and other pl
cians in past and future policy d
erations in this area has been less
by the perception among some l
lators that each group supports
vested interests of its members.
example, the American Colleg
Radiology is on record in suppo
a ban on physicians' self-refer
whereas the American Academ
Neurology opposes it.[17] In my vie
we respond to these issues refl
and defensively, or with platit
that are thinly veiled attempt
shield our special interests in
designed "safe harbors," then we
nothing less than losing our pla
the table of communal debate.

One is reminded of recent his
in the United Kingdom that rec
exactly this turn of events. Wh
became clear in 1987 that the poli
price of cost-containment in the
had become too high, that care ir
NHS based on professionally def
needs rather than individual w
tended to be perfunctory, and
nearly 1 million people were ir
queue for elective surgery,
Thatcher government responde

criticism by the presidents of the Royal Colleges by initiating a comprehensive review of the NHS. This process led to the establishment in April 1991 of a radically different NHS, including the privatization of many aspects of medical care. Against all precedent, not only was the medical profession itself excluded from the review process, but also those consulted were selected precisely because they did not reflect prevailing professional opinion.[18]

CONCLUSIONS

Given that cost-containment is a key policy objective in the US health system, as in the recently inaugurated Medicare physician payment mechanism, it is essential that neurologists join other health professionals, health services researchers, and public health workers, among other groups, to conduct an informed dialogue with the public to delineate the points at which the canons of good economics and good neurologic care differ. For example, a carefully performed physical and neurologic examination has recently become a *loss leader* in some practices, as an unforeseen consequence of Medicare pricing. (A loss leader is a retailing strategy that sells certain heavily advertised items below cost, hoping that the customer will stay to buy other, regularly priced merchandise.) Clearly, there is no place for leader pricing in moral patient care, and yet some physicians have little choice but to supplement lengthy cognitive patient encounters with self-referred laboratory tests and procedures, when Medicare payments for cognitive services fail to cover practice costs. In my view, however, if we are to maximize our credibility and effectiveness as professionals in this debate, the public must discern that we have subordinated self-serving interests for the common good. Accordingly, I suggest that the following steps merit thoughtful and open-minded attention by all neurologists.

First, individual neurologists and professional organizations should link forces with other specialties to develop joint consensus statements concerning financial and entrepreneurial matters; when that is not possible because of conflicting self-interest, then our best course by far is to maintain a public posture of abstention. Second, we should be supportive of technology assessment efforts, make proper use of assessment information in medical decision making, and insist that medical students and residents receive much more instruction in the fields of health services research, including the appropriate use of neurotechnology in ambulatory care. Third, we need to examine the relationship between an enlarging supply of practicing neurologists, the burden of neurologic illness in the entire population to be served, and the pressure on recently graduated practitioners to use privately owned technology to ensure the financial survival of their neurologic practices. Fourth, we should support a program of technology-neutral physician payment reform that addresses the imbalance between payment for time and effort spent in cognitive neurology vis-à-vis procedural neurology.

Finally, and probably most important of all, neurology should clearly and unambiguously separate itself from the "medical-industrial complex."[19] To retain our long-standing social contract with society, we must publicly declare that neurologists should derive their incomes from professional services, and not from entrepreneurial interests in the health care field. We should support the public ownership of elaborate technology to the greatest extent possible,[20] avoid new investments in business ventures that undermine the process of publicly guided technology diffusion, and undertake divestiture of those business arrangements and promotional advertising that enable critics to label us vendors. If we adhere to our recent course, I am concerned that our autonomy as trusted professionals will be progressively eroded, as it has been in the recent past, and that the young cohorts of neurologists we are training for practice in the 21st century will find themselves viewed by society as everyday business people in a commercial market, without the special advantages and privileges we have traditionally enjoyed in exchange for our special moral commitment. Clearly, we have the means at our disposal to guide our patients through the health care marketplace in the most humane and cost-effective way, if we elect to do so.[21]

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6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: Either 200 mg b.i.d. for tablets or 1 teaspoon q.i.d. for suspension (400 mg per day). Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: Either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension (200 mg per day). Increase at weekly intervals by adding up to 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg/daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 58887-052-30
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 58887-052-32

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

Bottles of 100	NDC 58887-027-30
Bottles of 1000	NDC 58887-027-40
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 58887-027-32

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture. Dispense in tight container (USP).

Suspension 100 mg/5 ml (teaspoon)—yellow-orange, citrus-vanilla flavored

Bottles of 450 ml	NDC 58887-019-76

Shake well before using.

Do not store above 86°F.

Dispense in tight, light-resistant container (USP).

Printed in U.S.A. C91-50 (Rev. 11/91)

BASEL Pharmaceuticals

BASEL Pharmaceuticals
Division of
CIBA-GEIGY Corporation
Summit, New Jersey 07901

Dosage Information: Tablets and Suspension

Indication	Initial Dose		Subsequent Dose		Maximum Dose
	Tablet	Suspension	Tablet	Suspension	Tablet or Suspension
Epilepsy 6-12 years of age	100 mg b.i.d. (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 100 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 1 teaspoon (100 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours
Over 12 years of age	200 mg b.i.d. (400 mg/day)	1 teaspoon q.i.d. (400 mg/day)	Add up to 200 mg per day at weekly intervals, t.i.d. or q.i.d.	Add up to 2 teaspoons (200 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours: 12-15 years 1200 mg/24 hours: over 15 years 1600 mg/24 hours: adults, in rare instances
Trigeminal Neuralgia	100 mg b.i.d. on the first day (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 200 mg per day in increments of 100 mg every 12 hours	Add up to 2 teaspoons (200 mg) per day q.i.d.	1200 mg/24 hours

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Hydrocephalus Following Spinal Cord Schwannoma Resection

Linda I. Bland, MD, Joseph V. McDonald, MD

• **We describe a patient who developed signs and symptoms of intracranial hypertension immediately after complete excision of a benign spinal cord schwannoma located at C3-4. We also present a brief review of the literature on the association of hydrocephalus with spinal cord tumors.**
(*Arch Neurol.* 1992;49:882-885)

Only 1% to 3% of patients with spinal cord tumors will present with signs and symptoms of intracranial hypertension in the form of papilledema and/or hydrocephalus.[1,2] Surgical excision of the intraspinal lesion, in the absence of leptomeningeal metastatic disease, is therapeutic for eradicating the signs and symptoms of intracranial hypertension in the majority of cases.[2-4] The association of hydrocephalus with benign extramedullary spinal cord tumors is particularly rare. We present an unusual case in which a patient developed symptoms of hydrocephalus immediately after complete removal of a C3-4 benign schwannoma, necessitating the placement of a ventriculoperitoneal shunt, which relieved the symptoms of intracranial hypertension.

REPORT OF A CASE

History

A 58-year-old right-handed man noted the onset of numbness and weakness in his right arm in January 1990. An examination at another institution demonstrated mild weakness in the right upper extremity (4/5 strength) with decreased sensation to pinprick of C-5 and C-6. A suboptimal cervical myelogram was obtained; the cerebrospinal fluid (CSF) protein level was elevated (0.57 g/L), and the red blood cell count was 89×10^6/L. A cervical spine roentgenogram revealed marked widening of the right C3-4 neural foramen (Fig 1). A magnetic resonance imaging (MRI) scan documented a 3.0×1.5-cm lesion that was isointense on T_1-weighted images and showed high-signal intensity on T_2-weighted images extending through the right neural foramen into the spinal canal at C3-4 on the right. The lesion enhanced homogeneously with gadolinium and displaced the spinal cord to the left, obliterating the subarachnoid space (Fig 2). The patient underwent a C2-4 laminectomy with complete removal of an intradural-extradural benign schwannoma (Fig 3) on January 18, 1990. Facetectomies and foraminal dissection of C3-4 under microscopic visualization facilitated the complete resection of the extradural component of the tumor. The spine was then fused with wiring of C-3 to C-4 on the left. On the second postoperative day, the patient complained of severe headaches that he had not experienced prior to surgery. The headaches did not abate, and were attributed to a CSF leak.

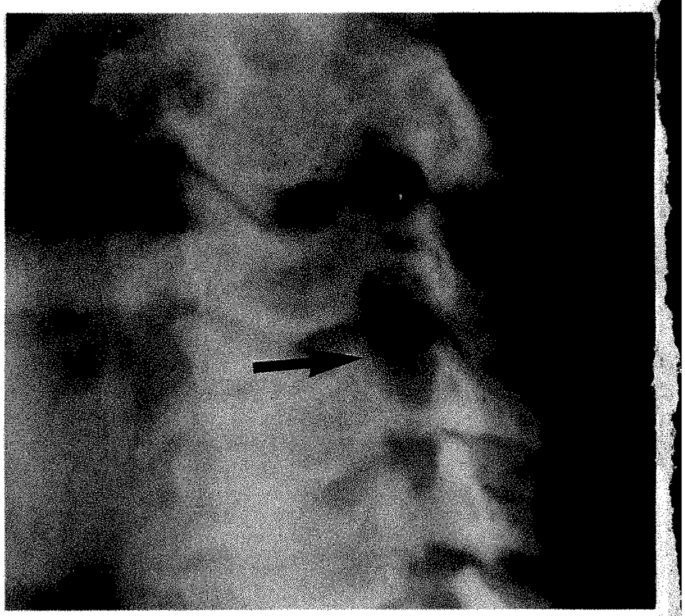

Fig 1.—*Cervical spine roentgenogram depicts marked widening of the right C3-4 foramen (arrow).*

The patient was discharged home, and came to Strong Memorial Hospital, Rochester, NY, on March 9, 1990, with a 1-montl history of decreased memory, confusion, dizziness, worsening o his headaches, emesis, abdominal distention, and flatulence.

Physical Examination

The patient was normotensive, and the findings of his general physical examination were unremarkable. The neurologic examination demonstrated mild diopter 1 papilledema bilaterally with some limitation of upward gaze, mild hypalgesia on the right at C-4 and C-5, an ataxic broad-based gait, confusion, disorientation, mild lethargy, and a right Babinski's sign.

Radiologic Studies

An MRI scan of the brain obtained March 10, 1990, showe ventriculomegaly of the lateral, third, and fourth ventricles wit prominent aqueductal flow void. On the T_1-weighted image, ther

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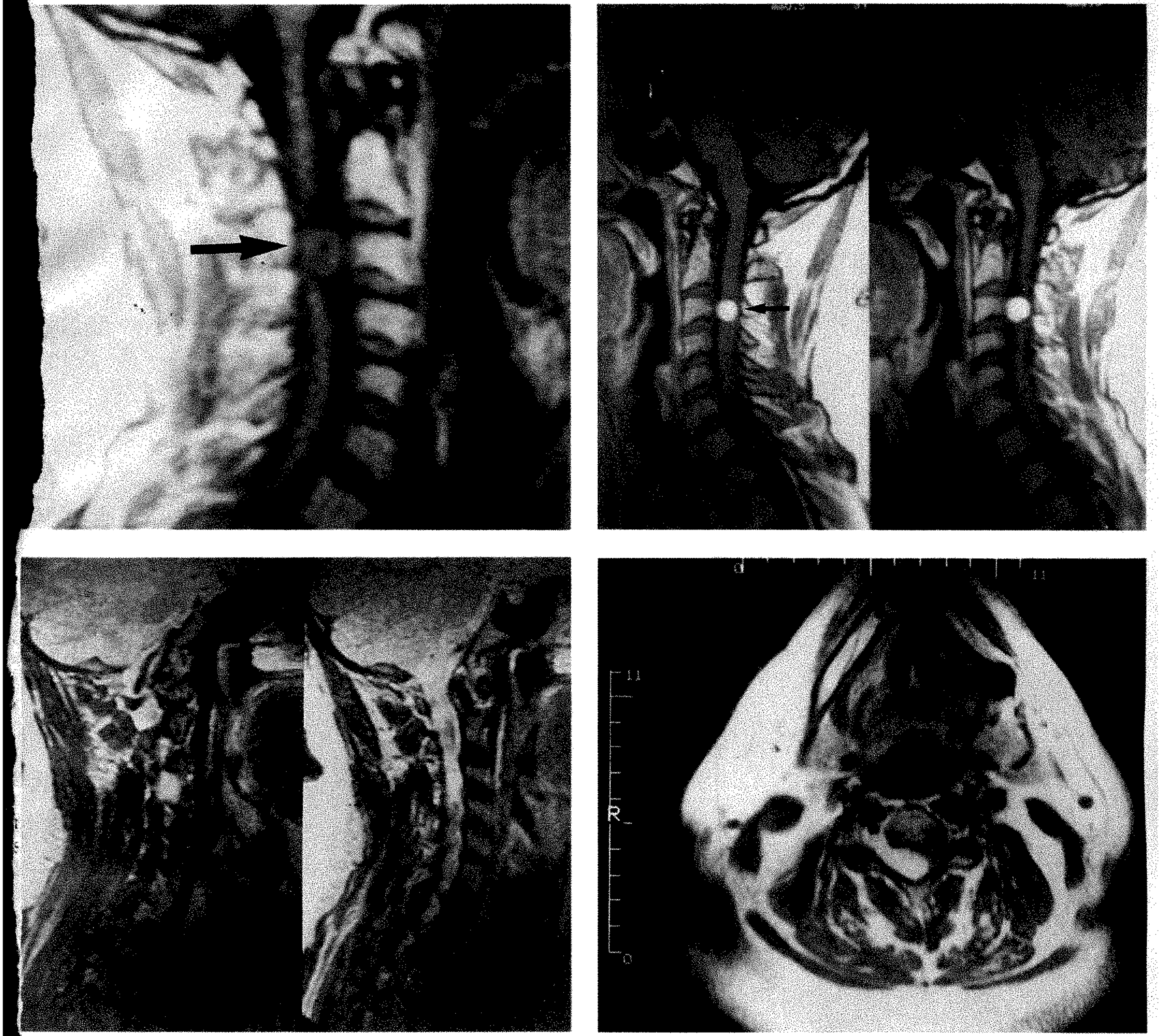


Fig 2.—*Magnetic resonance images of cervical spine. Top left and top right, Sagittal T_1-weighted image shows isointense lesion (arrow, top left) ex- ending through the right C3-4 neural foramen, which enhances with gadolinium (arrow, top right). Bottom left, Sagittal T_2-weighted image shows high-signal intensity lesion on the right at C3-4 (arrow). Bottom right, Coronal T_1-weighted image. The right C3-4 lesion enhances with gadolinium nd displaces the spinal cord to the left.*

vas high-signal intensity in the immediate periventricular white natter that could be consistent with fibrosis or transependymal dema. The T_2-weighted image was negative for siderosis and other intraparenchymal lesions (Fig 4). An MRI scan of the cervical spine obtained March 10, 1990, showed an enlarged right C3-4 neural foramen with high-signal intensity of the cord at C3-4 on the T_2-weighted image, reflecting postoperative gliosis, and high-signal intensity on the T_1- and T_2-weighted images within the neural foramen, consistent with a fat graft. There was no mass effect on the right vertebral artery or evidence of recurrent tumor when gadolinium was administered (Fig 5).

Operation

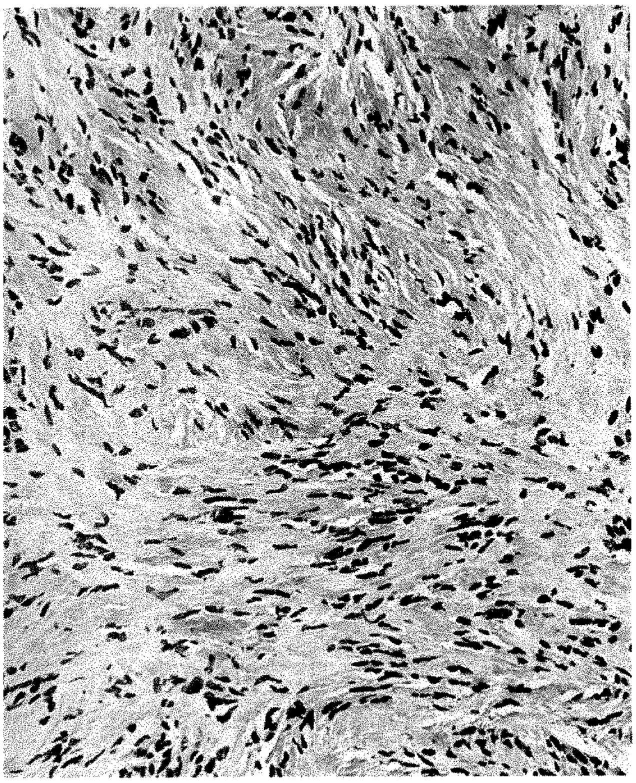
The patient was taken to the operating room for placement of right ventriculoperitoneal shunt with a medium-pressure Pu- enz valve. When the ventricle was tapped, the CSF shot out of he catheter, indicative of intracranial hypertension. The intracra- ial CSF pressure, even with hyperventilation and the loss of some CSF, was 230 mm of water with the patient in the supine position.

Postoperative Course

The patient was more alert, coherent, and oriented the day after his surgery. His ataxia, dizziness, emesis, and headaches resolved. A postoperative computed tomographic scan of his head obtained April 25, 1990, showed good position of the ventriculoperitoneal shunt within the right occipital horn and a marked decrease in hydrocephalus, with the ventricles being essentially normal in appearance. On June 1, 1990, the patient returned to work.

COMMENT

The association of hydrocephalus with intraspinal lesions is rare. There are 60 reported cases of intramedullary spinal cord tumors occurring with hydrocephalus, 27 (45%) of which were histologically malignant (grade III or



ig 3.—*Photomicrograph demonstrating that the cervical C3-4 lesion is schwannoma (hematoxylin-eosin, original magnification ×250).*

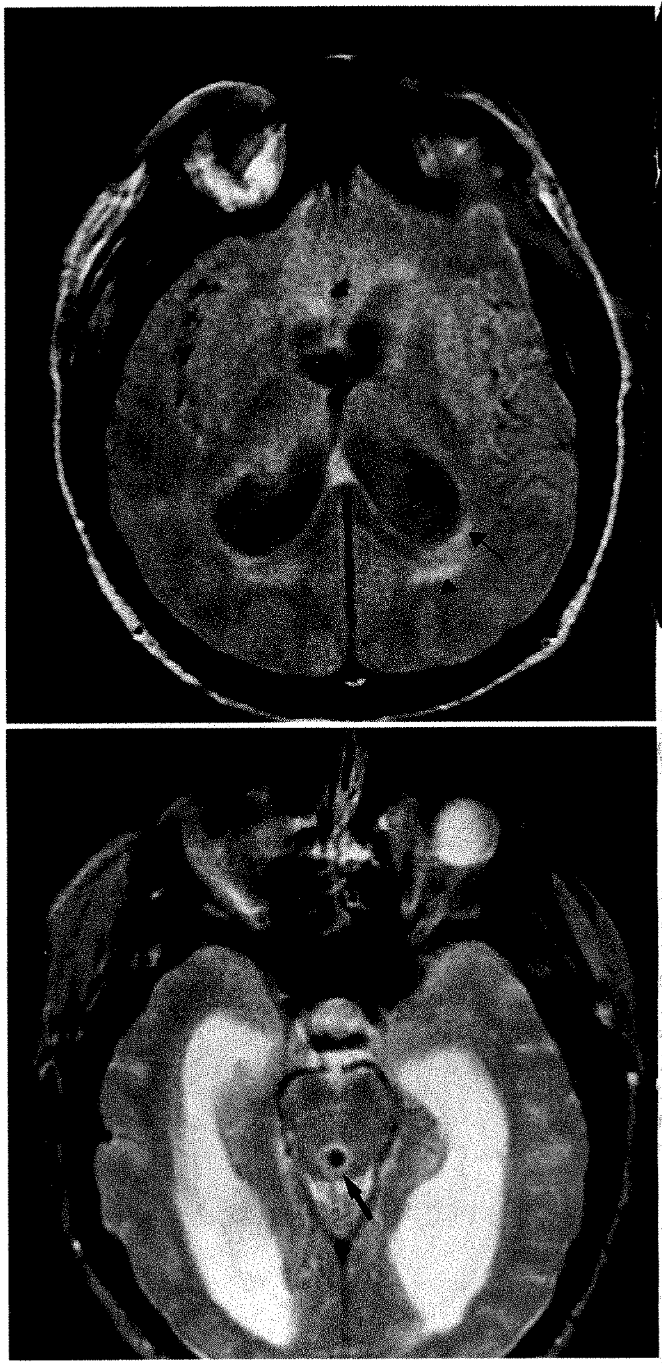


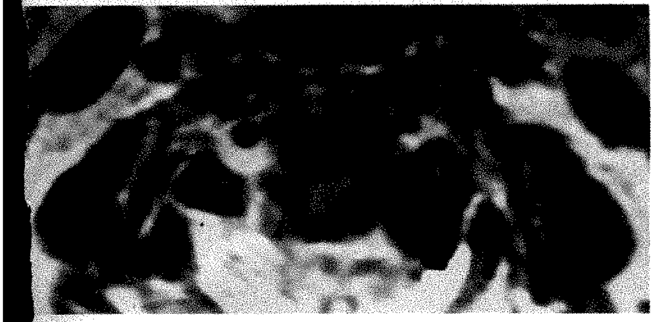
Fig 4.—*Magnetic resonance images* of the head. *Top, T_1-weighted image depicts hydrocephalus of low-signal intensity with high-signal intensity in both the periventricular (arrow) and intraparenchymal regions (arrowhead) that could represent gliosis or transependym edema. Bottom, T_2-weighted image demonstrates a patent aqueduct o Sylvius (arrow) and the absence of siderosis and other intraparenchyma lesions.*

V); the most common tissue diagnoses were ependymoma nd astrocytoma.[1,2,5-8] The association of hydrocephalus ith benign extramedullary spinal cord tumors is particlarly rare, with only 27 cases having been documented, to ur knowledge. Only 10 other cases, in addition to ours, of pinal cord neurinoma have presented with hydrocephlus. Meningioma, neurofibroma, and dermoid cyst in asociation with hydrocephalus have been reported in eight, ix, and three cases, respectively.[1,2,3,9]

Typically, patients will exhibit features of both clinical yndromes simultaneously, thus presenting with back or eck pain and radicular and/or myelopathic symptoms in onjunction with headache, dementia, and/or visual hanges. Yet symptoms of increased intacranial pressure ften predate those referable to spinal cord pathology in 0% to 50% of cases.[2,8,10] Complete excision of the spinal ord tumor results in eradication of ventriculomegaly as ocumented by computed tomography of the head, in orrection of papilledema, and in amelioration of the ymptoms of intracranial hypertension in the majority of ases, thereby eliminating the need for a shunting procedure.[2-4]

A plethora of pathophysiologic mechanisms have been uggested to explain the occurrence of hydrocephalus with pinal cord tumors, including hyperproteinrrhachia, spinal subarachnoid hemorrhage, mechanical obstruction, pidural venous compression, congenital association, metastatic disease, hyperviscosity of the CSF, and oincidence.[2,5,6,8-19] In our patient, the CSF was colorless and had an elevated protein count of 0.57 g/L and a red blood ell count of 89×10^6/L prior to removal of the cervical chwannoma. Although the development of hydrocephalus secondary to spinal cord tumors is clearly multifactorial, it is largely reversible. Complete excision of histologically benign intramedullary (grades I and II) and extramedullary spinal cord tumors results in the eradication of hydrocephalus and papilledema in the majority of cases.[2,3,10,18]

Our case is unique in that it represents the only documented case (to our knowledge) of an acute clinical onset of intracranial hypertension after complete remova of a benign spinal cord tumor, necessitating the placemen of a ventriculoperitoneal shunt, which relieved the symp



*5.—Magnetic resonance T_1-weighted image of cervical spine
anced with gadolinium demonstrates an enlarged right neural fora-
at C3-4 containing high-signal intensity consistent with a fat graft
ow). There was no evidence of recurrent tumor, as shown by the lack
nass effect on the right vertebral artery (small arrowhead) and the
ence of cerebrospinal fluid (large arrowhead) surrounding the right
of the spinal cord; an enhancing lesion was not present.*

ns of intracranial hypertension. The only other cases of
rocephalus developing after operative management of
spinal neoplasms were reported by Rifkinson-Mann
l[8] and Cohen et al[11] in their articles on malignant astro-
tomas (grades III and IV) of the spinal cord. However,
e majority of the patients in their series underwent
iopsies and subtotal resections with subsequent radia-
on therapy, and 62% of the patients had roentgeno-
aphic and autopsy evidence of leptomeningeal meta-
atic disease.

In our patient, an MRI depicting hydrocephalus with
nlarged lateral, third, and fourth ventricles and a patent
queduct of Sylvius in conjunction with the clinical find-
gs of papilledema and intracranial hypertension sug-
ested a diagnosis of acquired, communicating hydro-
phalus that became clinically active immediately after
section of a cervical schwannoma. Based on radiologic
udies, it is impossible to determine if the patient had
symptomatic ventriculomegaly that predated the onset of
is radicular symptoms. Both hyperproteinrrhachia and
barachnoid hemorrhage may have been etiologic factors
the development of hydrocephalus in our patient. It is
nlikely that an occult tumor in the posterior fossa was re-
ponsible for the development of hydrocephalus, since
here was no evidence of a lesion or mass effect on the
urth ventricle, basal cisterns, or sylvian aqueduct on the
$_2$-weighted MRI images. Clinically, the patient has re-
ained asymptomatic 1.5 years following the shunting
rocedure. Since gadolinium was not administered, it is impossible to rule out basal arachnoiditis secondary to irritation of the meninges by subarachnoid blood as an etiologic factor in the development of hydrocephalus. Our case demonstrates that the acute onset of headaches and/or emesis after spinal cord tumor resection, usually attributed to a postoperative CSF leak, may be secondary to associated intracranial hypertension, and merits a thorough clinical and radiologic workup.

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Professional Opportunities

CHARLOTTE, NORTH CAROLINA: High quality group of five neurologists all of whom are subspecialized, seeks to add another well-trained neurologist. Contact: Fred Pfeiffer, MD, 1900 Randolph Road, Suite 1010, Charlotte, NC 28207. Or call: (704) 334-7311.

NEUROLOGIST, BC/BE with strong clinical skills to join two neurologists and part-time neuropsychologist in southeastern Wisconsin. Located thirty minutes south of Milwaukee and sixty minutes north of Chicago on Lake Michigan. Rapidly expanding practice. Salary competitive and commensurate with experience. Contact: Raymond J. Rybicki, MD, (414) 631-8550. Or send CV to: 3803 Spring Street, Suite 201, Racine, WI 53405.

FLORIDA: If you are a BC/BE neurologist interested in associating with a solo neurologist in a beautiful east central coastal Florida city, please send your CV to: John LoZito, MD, 1400 Pine Street, Melbourne, FL 32901.

CHARLOTTE, NORTH CAROLINA: Neurologist BC/BE with interest or experience in neurorehabilitation to join three person group emphasizing general neurology, general rehabilitation, and pain rehabilitation programs. Respond with CV to: Ronald C. Demas, MD, 2115 East 7th Street, Charlotte, NC 28204. Or call (704) 372-3714.

EXCELLENT OPPORTUNITY for BC/BE neurologist with strong clinical skills to join a rapidly expanding neurological group in the suburban Milwaukee area. Salary competitive. Expertise in sleep or EEG desired. Please contact: Box #844, c/o AON.

EXTRAORDINARY OPPORTUNITY – The University of South Florida and the Tampa General Hospital are combining resources to establish a Stroke Service and are recruiting a Service Director. Requirements: Board-eligible/-certified status, stroke expertise, and teaching/scholarly abilities. Rank, salary, and benefits negotiable dependent upon qualifications. Contact: Leon D. Prockop, MD, Chairman, Department of Neurology, (813) 974-2794. MDC Box 55, 12901 Bruce B. Downs Boulevard, Tampa, Florida 33612. USF is an affiliated equal opportunity employer.

JOIN A UNIQUE three-county practice, currently with four persons, in scenic eastern Pennsylvania. Each physician is based primarily in one of three medical communities but all share coverage, and, via computer, billing, scheduling, and other administrative functions of this consulting practice. Current members have strong academic credentials and cover all neurodiagnostic capabilities, including two (eventually three) MRI facilities. We are committed to good care and not only to income, but compensation is competitive, partially based on productivity, fringe benefits are generous, and eventual partnership is possible. You can live in suburbia, on a farm, or in an old mill house. Cultural activities abound, the schools are good, the streets are safe, and the local farm produce is the best in the country. Major metropolitan areas of Philadelphia, Baltimore and New York are all within one to three hours. Send CV to: Schuylkill Neurologic Associates, 700 Schuylkill Manor Road, Suite 3, Pottsville, PA 17901.

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Professional Opportunities

NEUROLOGIST: Excellent opportunity for board-certified/board-eligible neurologists to join twc existing neurologists in a stimulating, busy practice Marquette General Hospital is a 321-bed regiona referral center, with a comprehensive neurophsi ology department and state-of-the-art technolog that includes magnetic resonance imaging and C scanning, and a hospital-based family practic residency. Medical students from Michigan Stat University's College of Human Medicine are reg larly assigned to the hospital and offer an opportu ty for teaching. Marquette General Hospital and i medical staff are committed to building a center c excellence in the neurosciences and have th necessary financial resources. The development these services will require the leadership and co operation of physicians in the field of neurology neurosurgery, psychiatry, physical medicine and rehabilitation. Salaried and private practice positions are available. If this special opportunity is of interest to you, please send CV to: Robert J. Raica, Marquette General Hospital, 420 West Magnetic Street, Marquette, MI 49855.

Neurologist

Outstanding practice opportunity for board-certified/-eligible adult neurologist to join department of neurology and neurosurgery in large multi-specialty group in summer of 1993. State-of-the-art electrodiagnostics, CT, MRI. Clinic is located in desirable coastal California community and is a regional referral center affiliated with major teaching hospital. Individuals with experience, board-certification/-eligibility in EEG and evoked potentials preferred. Send CV with reply to:

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TEXAS – NEUROLOGY + OTOLOGY: Chance of a lifetime for a neurologist specialized in, or interested in, specializing in vertigo and balance problems. A well-established neurologist in a 20 year old practice limited to otology and neurotology has developed a technique, using a laser in the inner ear, to bring vertigo into check without damaging the hearing – "the last unaddressed frontier in ear surgery" – and is interested in creating a team approach with the addition of a neurologist to his practice. The commitment is to first quality services, diagnosis, medical and surgical treatment of ear disease, and the need is for further expertise in the diagnosis and treatment of patients with balance problems, facial nerve abnormalities, Menire's disease, and otologic problems. Contact: Diana McClure, Cejka & Company, 222 South Central, Suite 400, St. Louis, MO 63105. (800) 678-7858, FAX: (314) 726-0026.

SOUTHEAST – Two neurologists, BC/BE, to establish practice on hospital campus. Generous income guaranteed for two years. Large referral base, catchment area population of 350,000. All neuro-diagnostic modalities needed. Proficiency ir EMG, EEG, CT, and MRI preferred. Inpatient anc outpatient experience necessary. Metropolitai community offers many cultural, academic, anc recreational activities. Yes, it's still possible to have it all: a thriving practice in supportive medical community, affordable lifestyle, mild climate, and Atlanta is two hours away. Immediate openings. For more information, call: Nancy Stallings, CompHealth, (800) 328-3044. 4021 South 700 East, Suite 300, Salt Lake City, UT 84107.

HAWAII

Excellent opportunity for BE/BC neurologist with experience in EEG, EMG, and EP to join well established multi-specialty group of 270 physicians. Modern and well-equipped 205-bed hospital with full diagnostic facilities, including MRI. Kaiser Permanente, Hawaii's oldest and largest HMO, offers competitive salaries and a comprehensive benefit package which includes medical, dental, retirement, profit sharing, moving allowance, and malpractice coverage. Live in paradise surrounded with spectacular beaches and an exceptional climate all year round. Enjoy an abundance of outdoor and water activities.

Please send CV to:

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Southern Coast of Maine

Adult or child BC/BE neurologist to join solo neurologist in private practice. This rapidly growing practice is located in an outstanding area which hosts the summer "white house". With community schools rated among the top school systems in the country, the area also has many outdoor recreational pursuits. Water sports (lake or ocean sailing, windsurfing, kayaking, canoeing, fishing, deep sea fishing, whale watching) and mountain hiking, biking, skiing and snowboarding are close by. Private residences are located in unspoiled developments or secluded areas along the unparalleled beauty of the Southern Maine Coast with its lighthouses, quaint fishing villages, and home to craftsmen and artists. Located 25 minutes from Portland, which has an international airport, symphony and other cultural opportunities and an hour and a quarter from Boston, this unique practice is supported by state-of-the-art electrodiagnostic (EMG, Evoked Potential, EEG) and neuroradiologic equipment (CT, MRI, Doppler) with a large referral base. Salary and benefits with partnership option based on qualifications. Send CV and three references to:

Mitchell K. Ross, MD
Park 111 Professional Building
407 Alfred Road
Biddeford, ME 04005

Professional Opportunities

RESORT COMMUNITY of Escanaba, Michigan, seeks a neurologist to establish a practice in a 50,000 population service area, currently without a neurologist. A confident generalist will have the opportunity to be immediately productive with support from the medical community and St. Francis Hospital. New hospital in gorgeous community with lakes, forests, boating, hiking and sports throughout the year. Contact: Dawn Hamman, Saint Francis, Inc., 4541 North Pospect, Suite 400, Peoria, IL 61614. (800) 232-3129.

EXCELLENT OPPORTUNITY

for BC/BE neurologist to practice at Allegheny General Hospital in Pittsburgh, Pennsylvania. Opening for July 1993 for private practice with geographic full-time appointment to the Medical College of Pennsylvania. Teaching and research opportunities with fully accredited residency in Neurology. Subspecialty in movement disorders or neuro-oncology preferred but not required. Subspecialty certification in EMG/muscle disease is highly desirable.

Inquire to Jon Brillman, MD or forward CVs to:
409 Baumer Street, Pittsburgh, PA 15209.

NEUROLOGIST – Board-eligible or board-certified, wanted to relocate to the fastest growing area in southwest Florida and one of the highest income areas in the U.S. We're looking for an energetic professional desiring to practice high quality medicine in a setting that will support your practice, as well as offer the opportunity to work with over 100 highly trained referring professionals. For more information, write to: Box #843, c/o AON.

SEEKING BC/BE neurologist with interest in stroke, dementia, sleep or EEG to join two physician group practice located within one hour of the metropolitan Chicago area. Early partnership. Salary negotiable. Subspecialty training in EEG or sleep preferable. Please contact: Box #845, c/o AON.

NEUROLOGIST

BC/BE with strong clinical skills to join busy well established multi-office neuroscience group in close proximity to Washington DC. Position available immediately, with competitive salary and benefit package. Send CV to:

Cheryl Henry, Administrator
VIRGINIA NEUROLOGIC CENTER
2836 Duke Street, Alexandria, VA 22314

VIRGINIA – We are seeking a personable, clinically-oriented, BC/BE neurologist to join a group of four neurologists located in the Shenandoah Valley. Clinical experience in EMG, EEG, Doppler, CT and MRI desirable. 400-bed hospital with full neurodiagnostic laboratory and CT/MRI imaging center. Send cover letter describing yourself and copy of your CV to: Winchester Neurological Consultants, 125-A Medical Circle, Winchester, VA 22601. Attention: G. Steele.

PEDIATRIC NEUROLOGIST: BC/BE pediatric neurologist to join established, 120-physician multi-specialty clinic located in beautiful northwest Arkansas. Holt-Krock Clinic, the 28th largest free-standing clinic in the nation, serves a patient base of 400,000 in Arkansas and Oklahoma. No other pediatric neurologist within 100-mile radius. We offer a guaranteed salary with full partnership in 2 to 2½ years, plus excellent fringe benefits. 680-bed hospital and new rehab hospital two blocks from main clinic. Must be willing to share call with adult neurologist, do testing consisting of EEG, EMG, evoked response, and cervical vascular ultrasound procedures. For details regarding this opportunity, send letter and CV to: Josephine Decker, Associate Administrator, Holt-Krock Clinic, 1500 Dodson Avenue, Fort Smith, AR 72901. (501) 782-2071.

PLEASE NOTE – Address replies to box number ads as follows: Box number ________ , c/o AON, P.O. Box 1510, Clearwater, FL 34617.

New Hampshire

Concord Hospital, a 295-bed acute care facility, located in the state capital of New Hampshire, is currently seeking a neurologist to fill the growing needs of the residents of Concord and the Merrimack Valley. Become a third associate in a group offering many benefits including health, disability and malpractice insurance.

Candidates must be board-certified/board-eligible, and have strong clinical interests. Experience and interest in EMG and evoked potentials preferred.

A designated Level II Trauma Center, over 174 physicians serve as members of the hospital's active medical staff. A full range of up-to-date neurodiagnostic equipment is available including MRI, CT scanners, as well as equipment for EMG, EP, EEG, and transcranial and carotid dopplers. Neuroradiologist and four neurosurgeons on staff.

Geographically located at the center of the state and just one hour from Boston, Concord is easily accessible to a wide variety of recreational and cultural activities. New Hampshire residents are not subject to a state income or sales tax.

Interested candidates please send CV to:

Jodie Cavanaugh, Coordinator
Physician Services
Concord Hospital
250 Pleasant Street, Concord, NH 03301

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Professional Opportunities

MISSOURI – State-of-the-art, 200-bed hospital seeks BC/BE neurologist to take over the practice of a physician leaving for academic position. Enjoy living in the beautiful, tree-covered hills of southern Missouri. This is a sportsman's paradise with ideal hunting and fishing area nearby. Salary of $130,000 to $150,000 plus benefits. Send CV or call: Keith McGuire, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 11991, Atlanta, GA 30346. Telephone: (800) 544-1987.

Positions Available

ADULT NEUROLOGIST – Three-person, successful neurology group in beautiful Pennsylvania suburban community seeks additional member for clinical practice with academic affiliation. Teaching and research opportunities exist, subspecialty interest and/or fellowship desirable. Reply to: Box #840, c/o AON.

Positions Wanted

NEUROLOGIST – Board-certified with fellowship in geriatric neurology and Florida license, interested in relocating to Florida. Box #841, c/o AON.

Faculty Positions

MICHIGAN STATE UNIVERSITY Kalamazoo Center for Medical Studies (MSU/KCMS). The Pediatric Neurology Section of MSU/KCMS is seeking a second BC/BE pediatric neurologist. This faculty position is at the assistant professor level and has responsibilities for patient care and medical student/resident teaching. Emphasis on clinical activities including electrodiagnostics and epilepsy/seizures. MSU/KCMS serves as the largest pediatric referral center in southwestern Michigan with 24 pediatric subspecialists. Contact: Richard Katnik, MD, PhD, Director, Section of Pediatric Neurology, Pediatric Faculty Office, Bronson Medical Center, 252 East Lovell Street, Kalamazoo, MI 49007. (616) 341-8277.

ACADEMIC NEUROLOGIST. Albert Einstein College of Medicine/Montefiore Medical Center, Department of Neurology, section of neurophysiology is seeking an adult neurologist to join a comprehensive epilepsy program including an active surgical program. The position would be at either the assistant or associate professor level. The applicant must be board-eligible or -certified in neurology and clinical neurophysiology and have specialty training in epilepsy. The applicant should be capable of clinical or basic epilepsy research. Training in EEG and presurgical evaluation of patients is desirable. The candidate would have the opportunity to interact with a large group of basic and clinical neuroscientists and would be encouraged to develop an academic program. All interested applicants should send a curriculum vitae, letter of interest, and names of three references to: Dr. Solomon Moshe/Dr. Shlomo Shinnar, Montefiore Medical Center, Department of Neurology/EEG Lab, 111 East 210th Street, NW 7, Bronx, NY 10467. Albert Einstein College of Medicine/Montefiore Medical Center is an equal opportunity/affirmative action employer.

LOYOLA UNIVERSITY CHICAGO Stritch School of Medicine seeks Director of Stroke Program. Resources include transcranial Doppler, modern neuro-imaging laboratory with SPECT, and molecular neuroscience laboratories. Loyola University is a large center for cardiovascular disorders with very active surgical and cardiology programs. Research collaborations possible with cardiology and cardiovascular surgery. Candidates should be board-eligible or -certified neurologists with scholarly career interests and qualified for academic appointment. Send reply to: Gastone Celesia, MD, Chairman, Neurology Department, Loyola University Chicago, 2160 South First Avenue, Chicago, IL 60153. Loyola is an equal opportunity/affirmative action employer.

Faculty Positions

TEXAS TECH is searching for an academic electromyographer to join a busy laboratory: Well equipped, technically staffed. Teach residents and students. Seven neurologists, muscle-nerve biopsy laboratory, experimental neuropathologist. Contact: Joseph B. Green, MD, Department of Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

THIRD PEDIATRIC NEUROLOGIST needed for busy practice, new pediatric neurology fellowship program. Seven neurologists in department, five basic neuroscientists. Opportunity for collaborative research. Subspecialty interests encouraged. Contact: Joseph B. Green, MD, Department of Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

Practices Available

WELL ESTABLISHED busy neurology practice in major Kentucky city. Physician retiring. All medical specialties represented in office/hospital complex. Desirable cultural, educational, recreational advantages. Reply to: Box #847, c/o AON.

NEUROLOGICAL PRACTICE for sale – Close to Tampa, Florida. Local hospital 130 beds. $60K. Reply to: P.O. Box 101, Plant City, FL 33566.

Miscellaneous

PATIENT EDUCATION VIDEOS – Electomyography/$59.95, Nerve Conduction Velocity/$59.95, Thermography/$59.95, Somatosensory Evoked Potentials/$59.95, EMG & NCV/$99.95, Patient Spinal Education (Neck & Back Injuries)/$139.95, Neurodiagnostic Testing (All Inclusive)/$139.95. CODs, MC, VISA, Discover, call: (800) 332-7400. Check or money order to: Medfo, Inc., P.O. Box 7730, St. Petersburg, FL 33734. 30-day money back guarantee.

Neurobehavior Fellowship

Emory University School of Medicine invites applications for a one- or two-year fellowship in behavioral neurology, beginning on or after July 1, 1993. The fellowship will offer exposure to the neurology and neuropsychology of dementia, stroke, head injury, temporal lobe epilepsy, movement disorders, and atypical psychiatric disorders.

The fellow will be encouraged to intensively participate in one of the research activities of the program. Current clinical research includes drug trials for Alzheimer's disease, cognitive evoked potentials in aging and stroke, and the behavioral problems associated with temporal lobe epilepsy. Current basic research involves cellular neuroanatomy and neurophysiology relating to neuronal injury.

Please send letter of inquiry and CV to:

Robert C. Green, MD
Neurobehavioral Program
EMORY UNIVERSITY
DEPARTMENT OF NEUROLOGY
Wesley Woods Center
1821 Clifton Road, NE
Atlanta, GA 30329
Telephone: (404) 728-6682

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ICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) d complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage d Administration and Clinical Pharmacology in the full prescribing information).

NTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

RNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. n, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution lternative antiepileptic medication arises, this should be done gradually. However, in the event of an rgic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this e, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

here have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudo-mphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been blished, the occurrence of lymphadenopathy indicates the need to differentiate such a condition other types of lymph node pathology. Lymph node involvement may occur with or without symp-s and signs resembling serum sickness, eg, fever, rash and liver involvement.

n all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every rt should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease rum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

ge in Pregnancy: A number of reports suggests an association between the use of antiepileptic s by women with epilepsy and a higher incidence of birth defects in children born to these women. are more extensive with respect to phenytoin and phenobarbital, but these are also the most mmonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar sociation with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See "Warnings" section for information on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, and immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Caution – Federal law prohibits dispensing without prescription. 0362G280

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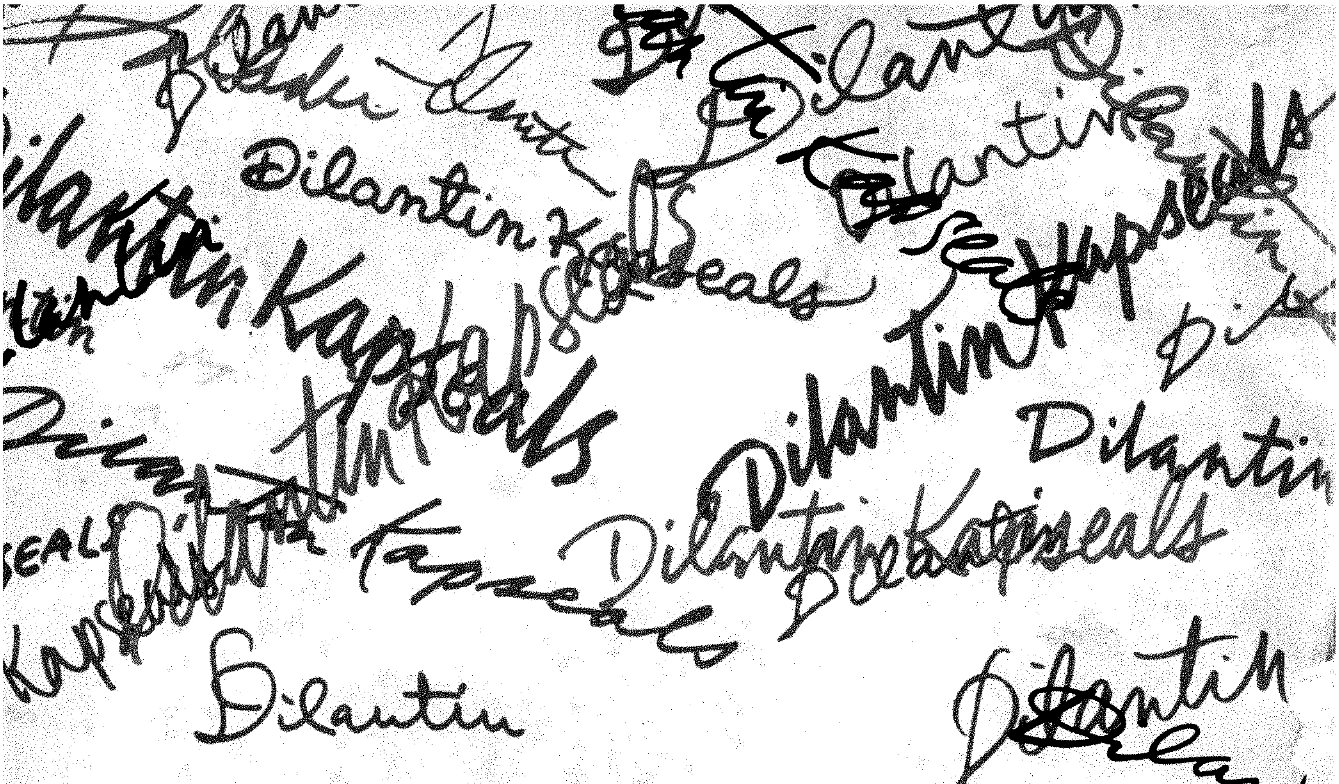

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